PROTOCOL SL75.14

VERSION 7.0 – 05 October 2017

A randomized, double-blind, placebo-controlled, multi-center study of the efficacy and safety of STG320 sublingual tablets of house

dust mite (HDM) allergen extracts in adults and adolescents with HDM-associated allergic rhinitis

Sponsor: STALLERGENES

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FRANCE

STG320 Sublingual Tablet of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* Allergen Extracts

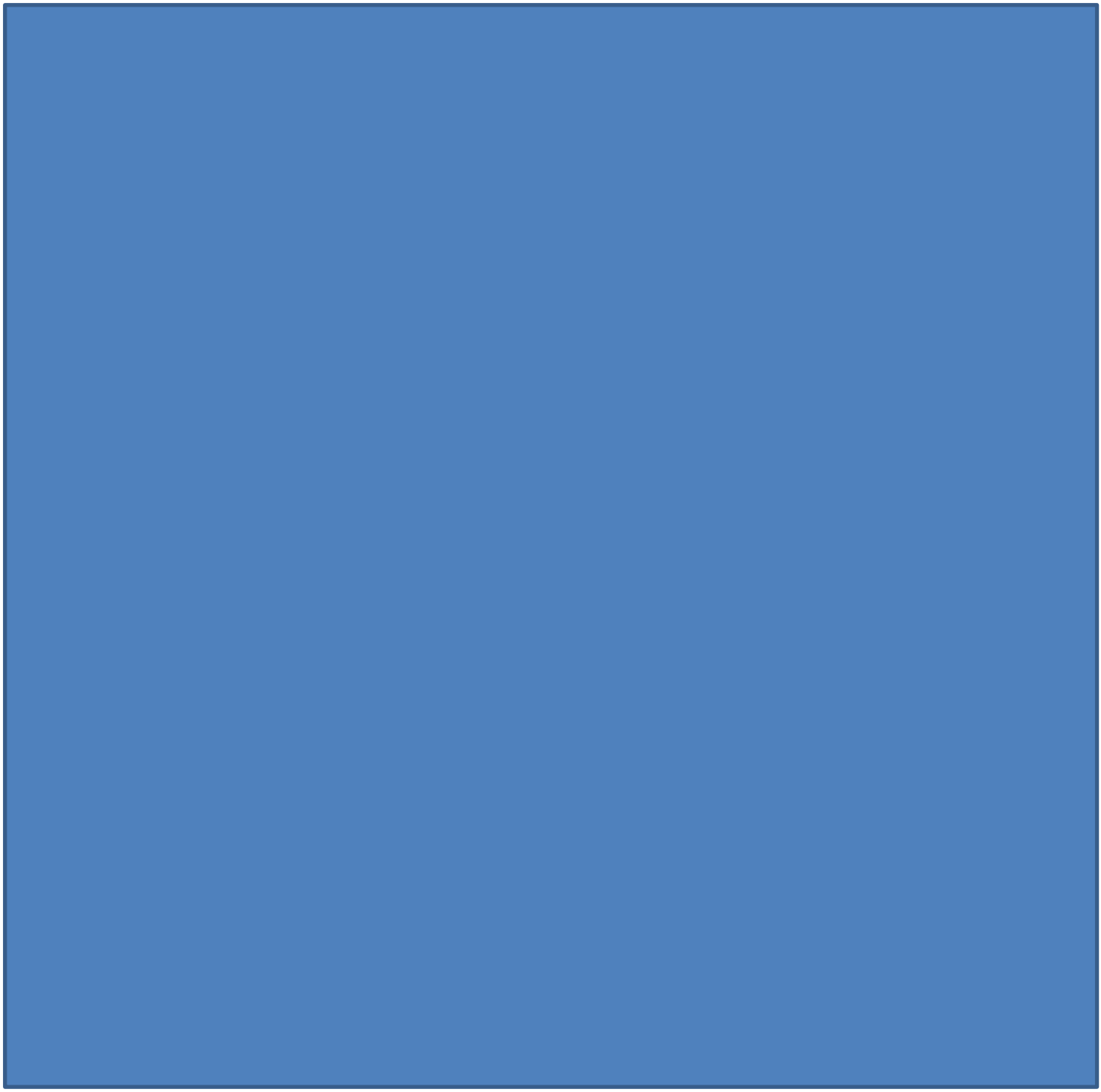
IND Number: 16252

EudraCT Number: 2014-004223-46

ClinicalTrials.gov ID: NCT02443805

Confidential/Proprietary Information

1. SIGNATURE PAGE



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- agree to promptly update this information if any relevant changes occur during the course of the study and for one year following completion of the study, and
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Obligations of confidentiality are accepted by both parties.

Investigator:

Name: _____

Study Site number: _____

Date: _____

Signature:

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3. GENERAL INFORMATION

3.1 Investigator

The complete and updated list of Investigators is maintained in the Trial Master File (TMF).

3.2 Sponsor

3.3 Contract Research Organization (including Central Laboratory)

3.5 Protocol Summary

Study number: **SL75.14**

Title of the study:

A randomized, double-blind, placebo-controlled, multi-center study of the efficacy and safety of STG320 sublingual tablets of house dust mite (HDM) allergen extracts in adults and adolescents with HDM-associated allergic rhinitis.

Study objectives:

To assess the efficacy and safety of 12 months of treatment with 300 IR of STG320 sublingual tablets compared with placebo in adults and adolescents with HDM-associated allergic rhinitis (AR).

Primary objective:

To evaluate the efficacy of STG320 sublingual tablets at a daily dosage of 300 IR when administered for 12 months to adults and adolescents with HDM-associated AR.

The primary efficacy variable will be the average Total Combined Score (TCS), calculated for each patient as the average of the non-missing daily TCSs during the primary evaluation period (i.e., the last 4 weeks of treatment). The daily TCS (scale 0-15) is the sum of the subject's daily Rhinitis Total Symptom Score (RTSS, scale 0-12) and daily Rescue Medication Score (RMS, scale 0-3).

Secondary objectives:

1) To assess the efficacy of STG320 sublingual tablets at the dosage of 300 IR as evaluated by the following secondary efficacy variables during the primary evaluation period:
   - Rhinitis Total Symptom Score (RTSS): itchy nose, sneezing, runny nose, blocked nose
   - Rescue Medication Score (RMS)
   - Adjusted Symptom Score (ASS)
   - Combined Symptom and Medication Score (CSMS)
   - Total Ocular Symptom Score (TOSS): itchy/red eyes and watery eyes
   - Rhinoconjunctivitis Total Symptom Score (RCTSS): four rhinitis symptom scores and two ocular symptom scores
   - Individual Rhinoconjunctivitis Symptom Scores (RSSs): itchy nose, sneezing, runny nose, blocked nose, itchy/red eyes and watery eyes
   - Rhinoconjunctivitis rescue medication use, overall and by type of treatment

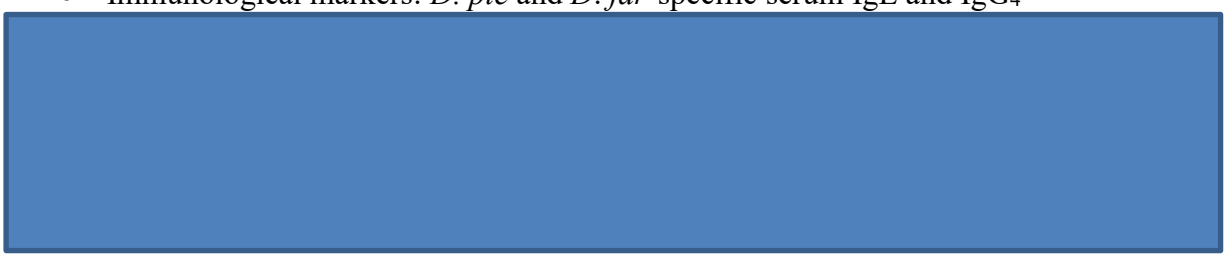
- Overall assessment of allergic rhinitis symptoms by a Visual Analogue Scale (VAS) (ranging 0-100)
- Proportion of Symptom Controlled Days (PSCD), Proportion of Not-Controlled Days (PNCD) and Controlled Patients (CP)
- Overall Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)≥12) and RQLQ(S)≥12 domains
- Health questionnaire EQ-5D-5L
- Global Rating of Change Score (GRCS) (15-point Likert scale)

2) Rhinoconjunctivitis symptom evaluation and rescue medication use will also be evaluated during the 2-week secondary evaluation periods (i.e., assessment to be started 2 weeks before the relevant visit at month 3, month 6 and month 9). The following endpoints will be assessed:

- TCS
- RTSS
- RMS
- ASS
- CSMS
- TOSS
- RCTSS
- RSSs
- Rhinoconjunctivitis rescue medication use, overall and by type of treatment
- Overall assessment of allergic rhinitis symptoms by a Visual Analogue Scale (VAS)

3) To assess the effect of STG320 on other variables at the end of the treatment:

- Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI + CIQ: AS)
- Immunological markers: *D. pte* and *D. far*-specific serum IgE and IgG_4



Safety objectives:

To assess the safety of 12 months of treatment with STG320 at the daily dose of 300 IR. The safety assessments include adverse events (AEs), Adverse Events of Special Interest (AESI) (anaphylaxis, severe laryngopharyngeal disorders, autoimmune disorders and eosinophilic esophagitis), vital signs and routine safety laboratory tests.

Methodology:

This is a randomized, double-blind, placebo-controlled, phase III study with two parallel arms in patients with house dust mite (HDM)-associated allergic rhinitis (AR).

The study consists of a screening phase (1 to 6 months), a treatment phase (12 months) and a post-treatment follow-up phase (2 weeks).

Study Type/Phase: III

Inclusion Criteria

The patient must fulfill the following inclusion criteria to be eligible for the study:

1. Have house dust mite (HDM)-associated allergic rhinitis (AR) (with or without asthma) for at least 1 year based on the presence of:
    - Symptoms for 4 or more consecutive weeks in the previous year and for at least 4 days per week during those weeks.
    - Symptoms requiring regular intake of symptomatic treatment(s).
    - Symptoms evaluated as "troublesome" by the patients or impairing their daily activities, leisure or sport, school or work or involving sleep disturbance.
2. Have given signed informed consent to participate, after having been informed of the nature and aims of the study, in accordance with local regulation and requirements.
3. Male or female outpatients 12 to 65 years of age.
4. Sensitized to D. pteronyssinus (*D. pte*) and/or D. farinae (*D. far*) defined as skin prick test wheal diameter at least 5 mm greater than the negative control and HDM-specific serum IgE ≥3.5 kU/L.
5. Willing to and capable of completing the e-diary, study questionnaires and scales.

Exclusion Criteria

If a patient meets any of the following criteria, s/he cannot participate in this study:

1. A history of rhinitis, rhinoconjunctivitis or asthma to allergens other than HDM, likely to result in rhinitis symptoms during the baseline and primary evaluation periods.

Specifically, when the following are present:

- documented sensitization (positive Skin Prick Test [wheal diameter at least 5 mm greater than the negative control] or allergen specific serum IgE ≥3.5kU/L) and history of clinically relevant symptoms to allergen(s) other than HDM
- anticipated exposure to such allergen(s) during the baseline and primary evaluation periods

For example, the following patients are to be excluded:

- patients sensitized to cat or dog allergens and regularly exposed to these animals
- patients sensitized to perennial allergens, such as aspergillus, cladosporium, alternaria, cockroach
- patients sensitized to seasonal allergens such as parietaria, ragweed or mugwort, if these allergens are endemic in the region during the baseline and primary evaluation periods

2. Any diagnosed nasal (other than HDM allergic rhinitis) or oral disease that could interfere with the efficacy or safety assessments, such as nasal polyposis, recurrent chronic rhino-sinusitis (at least 2 isolated episodes per year in the 2 previous years, each episode lasting more than 8 weeks) or a history of chronic oral inflammation or current active oral inflammation from any etiology (e.g., oral lichen planus, oral ulceration or oral mycosis) and/or oral wounds.
3. Recent nasal surgery (i.e., within the previous 6 months).
4. Partly controlled or uncontrolled asthma defined in the Global Initiative for Asthma 2014 guidelines (GINA 2014) as the presence of daytime asthma symptoms more than twice/week or nocturnal symptoms/awakening or need for reliever/rescue treatment more than twice/week or FEV_1 <80% of predicted or personal best value.
5. Asthma therapies consistent with GINA treatment Step 3, Step 4 and Step 5 i.e., the preferred controller medication consists of inhaled corticosteroid (ICS) combined with long-acting beta (β)-2 agonist (LABA) according to GINA classification 2014 (refer to *Appendix II* for the full details of other controller options).

   Eligible asthmatic patients will be those with asthma controlled by treatment(s) consistent with GINA 2014 treatment Steps 1 or 2 [i.e., reliever treatment with as needed short acting β2-agonist with or without controller treatment consisting of low dose inhaled corticosteroid (i.e., ≤400 µg of budesonide/day or equivalent dose of other corticosteroid) or leukotriene receptor antagonist or low dose theophylline].
6. Experienced a life-threatening asthma attack or an asthma exacerbation that resulted in Intensive Care Unit (ICU) hospitalization.
7. Requiring continuous treatment with systemic corticosteroids for any indication.
8. Requiring continuous treatment with β-blockers or with Monoamine Oxidase Inhibitors

(MAOIs).

9. Received an immunosuppressive treatment within 3 months prior to screening.
10. Received allergen immunotherapy (AIT) by any route:
    - for house dust mites: AIT for more than 1 month within the 5 years before screening
    - for other allergen(s): ongoing or recently stopped (within 6 months) AIT.
11. Any history of anaphylaxis after previous allergen immunotherapy, exposure to allergen(s) or of unknown cause.
12. A history of hypersensitivity to STG320 or its excipients or contraindication to the use of rescue medications (i.e., antihistamines and corticosteroids).
13. Female with positive urine pregnancy test or lactating or expecting to conceive within the duration of the study.
14. Sexually active female of child-bearing potential without medically accepted contraceptive method: hormonal birth control (orally, injectable or by implant, for at least 2 months before enrollment), intrauterine device, male condom or diaphragm used with spermicide, monogamous relationship with a vasectomised partner. Women are considered not to have childbearing potential prior to menarche or at least 2 years after menopause or if they have had a bilateral tubal ligation or a total hysterectomy or bilateral oophorectomy or ovariectomy.
15. Unable or unwilling to comply with the study protocol requirements, including those who anticipate significant changes in their daily environment in relation to HDM exposure or who are likely to travel for extended periods of time during the main efficacy assessment period.
16. Patients with past or current disease(s) which, as judged by the Investigator, may affect the patient's participation in or the outcome of this study. These diseases include, but are not limited to, cardiovascular disease, malignancy, active tuberculosis, hepatic disease, renal disease, hematologic disease, neurologic or psychiatric disease, severe autoimmune disorder, immunodeficiency or immunologic disease and endocrine disease.
17. Patients with a history of eosinophilic esophagitis or with current severe or persistent gastroesophageal symptoms including dysphagia or chest pain.
18. Contraindications to allergen specific immunotherapy.
19. Patients with history of drug or alcohol abuse.
20. Participation in any clinical study within 30 days prior to the selection visit.
21. Possible dependency of the patient on sponsor or investigators/subinvestigators or study personnel.

Patients who fulfill all of the above inclusion criteria and none of the exclusion criteria will be eligible for the 5-week placebo run-in period. During this period, patients will take placebo tablets (single-blind) and will score their HDM-associated allergic rhinoconjunctivitis symptoms and record rescue medication usage on a daily basis. The last 4 weeks will be used as the baseline evaluation period.

Inclusion Criterion at the end of the run-in/baseline evaluation period

Only patients who fulfill the following criterion will be eligible for randomization:

1. Patients with an average TCS ≥5 (on a scale of 0 to 15) over the baseline evaluation period.

Study period (planned)**:**

Study Duration:	June 2015 to June 2018
Time Schedule:	
First patient first visit:	June 2015
Screening Phase:	June 2015 to April 2016 and from September 2016 to June 2017
Baseline Evaluation Period:	September 2015 to May 2016 and from September 2016 to July 2017
Randomization Period:	October 2015 to May 2016 and from October 2016 to July 2017
Last patient last treatment:	June 2018 (projected)
Last patient last visit:	June 2018 (projected)

Number of patients (planned):

Approximately 3,500 patients will be screened to randomize 1,740 patients (i.e., 870 patients randomized in each treatment group).

Number of centers (planned):

Approximately 150-190 study centers in the United States of America, Canada, Europe, Israel and Russia are expected to participate.

Investigational product: *(dose, mode of administration)*

Investigational product: STG320 - Sublingual tablet of house dust mites allergen extracts (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*)

Doses: 300 IR

Mode of administration: STG320 is administered sublingually.

Two treatment steps:

1) Initiation Period:

During the initiation phase, patients randomized to the active treatment group will take 1 tablet of 100 IR on Day 1, and 2 tablets of 100 IR to be taken simultaneously on Day 2.

2) Maintenance Period:

From the 3rd day until the end of the Treatment Phase (approximately 12 months, with a minimum of 10 months), patients will take 1 tablet of 300 IR per day.

Reference product:

Reference product: placebo tablets matching the 100 IR dose in the initiation phase [100 IR placebo (P_{100})] and placebo tablets matching the 300 IR dose during the maintenance phase [300 IR placebo (P_{300})].

Mode of administration: Placebo STG320 is administered sublingually.

1) Initiation Period:

During the initiation phase, patients randomized to the placebo treatment group will take 1 tablet of 100 IR placebo (P_{100}) on Day 1, and 2 tablets of 100 IR placebo (P_{100}) to be taken simultaneously on Day 2.

2) Maintenance Period:

From the 3rd day until the end of the Treatment Phase (approximately 12 months, with a minimum of 10 months), patients will take 1 tablet of 300 IR placebo (P_{300}) per day.

Study duration per patient:

The total duration of the study for an individual patient will be between 14 and 20 months, including a 1 to 6 month screening phase (including a run-in period of 5 weeks), a treatment phase of approximately 12 months and a post-treatment follow-up phase of 2 weeks. In total, 10 visits will be conducted: 2 screening visits, 1 randomization visit, 6 regular follow-up visits (Months 1, 3, 6, 9, 11 and 12) and 1 post-treatment visit (Month 12.5).

Evaluation periods

The evaluation periods will be defined as follows:

- Baseline evaluation period: last 4 weeks of the 5-week run-in period
- Interim evaluation periods: 2 weeks every 3 months after randomization (i.e., Month 3, Month 6 and Month 9),
- Primary evaluation period: 4 weeks prior to the end of the treatment period

Criteria for evaluation:

Primary Efficacy Variable: Total Combined Score

The primary efficacy variable will be the average Total Combined Score (TCS). The average TCS is calculated for each patient as the average of the non-missing daily TCSs.

The daily TCS (scale 0-15) is the sum of the patient's daily Rhinitis Total Symptom Score (RTSS, scale 0-12) and daily Rescue Medication Score (RMS, scale 0-3).

The RTSS is defined as the sum of the four rhinitis symptom scores (i.e., itchy nose, sneezing, runny nose, and blocked nose) evaluated daily by the patient. The patient assessment will address symptom intensity over the previous 24 hours and will be performed at the same time every morning, using a 4-point scale (0 = no symptoms; 1 = mild symptoms (symptom clearly present, but minimal awareness; easily tolerated), 2 = moderate symptoms (definite awareness of symptom that is bothersome but tolerable), 3 = severe symptoms (symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping).

If any of the four individual rhinitis symptoms for a given day is missing, then the RTSS for that day will be considered missing.

The RMS is based on the assumptions that an intranasal corticosteroid is more effective than an antihistamine and an oral corticosteroid is more effective than an intranasal corticosteroid, leading to a derived ordinal scale: 0=absent, 1=oral associated or not with topical (ocular drops) non-sedative H1 antihistamine (H1A), 2=intranasal corticosteroids (INS) with or without oral or topical (ocular drops) H1 antihistamine, 3=oral corticosteroids with or without INS or oral or topical (ocular drops) H1 antihistamine.

If rescue medication data for a given day are missing, then the RMS for that day will be considered missing.

Secondary Variables

- Rhinitis Total Symptom Score (RTSS, scale 0-12).
- Rescue Medication Score (RMS, scale 0-3).
- Adjusted Symptom Score (ASS, scale 0-12). This score is derived from the daily RTSSs, after adjustment for the patient's rescue medication use.
- Combined Symptom and Medication Score (CSMS, scale 0-6). The CSMS is derived from RTSS and RMS.

- Total Ocular Symptom Score (TOSS, scale 0-6). The TOSS is calculated as the sum of individual scores for itchy/red eyes and watery eyes.
- Rhinoconjunctivitis Total Symptom Score (RCTSS, scale 0-18). The RCTSS is calculated as the sum of the four rhinitis symptom scores and the two ocular symptom scores.
- Each of the six individual Rhinoconjunctivitis Symptom Scores (RSSs, each scored on a scale of 0-3): itchy nose, sneezing, runny nose, blocked nose, itchy/red eyes and watery eyes
- Rhinoconjunctivitis rescue medication use, overall and by type of treatment
- Visual Analogue Scale (VAS) assessing the intensity of the allergic rhinitis symptoms (ranging from 0 = absence of symptoms to 100 = very severe symptoms).
- Proportion of Symptom-Controlled Days (PSCD) defined for each patient during the evaluation periods as:
  - $PSCD_{2\text{-}0}$: Proportion of days with RTSS ≤ 2 and no rescue medication used
- Proportion of Not-Controlled Days (PNCD) defined for each patient during the evaluation periods as the proportion of days with:
  - At least one individual rhinitis symptom score = 2 and RMS>0, or
  - At least two individual rhinitis symptom scores = 2 whatever the RMS, or
  - At least one individual rhinitis symptom score = 3 whatever the RMS
- Controlled patients (CP) as follows:
  - $CP75_{2\text{-}0}$: Patients with at least 75% of the days with RTSS ≤ 2 and no rescue medication used (controlled for at least three quarters of the evaluation periods)
- Overall Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)≥12) score and RQLQ(S)≥12 domain scores
  The RQLQ(S)≥12 consists of 28 questions, divided into 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms and emotions), each question being evaluated on a 7-point Likert scale (lower being better).
- EQ-5D-5L
  EQ-5D-5L describes the patient's health state using 5 questions and a VAS score.
- Global Rating of Change Score (GRCS): questionnaire assessing treatment efficacy by the patient compared to the baseline evaluation period (15-point Likert scale)

Other variables

- Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI + CIQ: AS)
- Immunological markers: *D. pte* and *D. far*-specific serum IgE and IgG_4

[redacted]

Safety variables:

Adverse events, Adverse Events of Special Interest (AESI) including anaphylaxis, severe laryngopharyngeal disorders, autoimmune disorders and eosinophilic esophagitis, assessment of routine laboratory safety tests, physical examinations and vital signs.

Study Conduct:

Screening Phase:

Visit 1 (Selection Visit):
Study patient information and informed consent form signature, demographics/ height/ weight, medical history, and prior and concomitant medication use, diagnosis of asthma and its treatment, FEV_1 for all patients (i.e., whether asthmatic or not), physical examination and SPT for HDM and other allergens, urine pregnancy test for all female patients of childbearing potential.
Testing of blood laboratory parameters and immunologic markers in patients with positive SPT.
[redacted]

Visit 2 (Run-in period Visit):
Patients meeting all the selection criteria will enter a single-blind placebo run-in period of 5 weeks (including the baseline evaluation period). This 5-week period is to be selected based on the patient's history of HDM-related rhinitis symptoms and the investigator's knowledge of the peak season for HDM in the area. During this 5-week period, patients will take 1 placebo tablet sublingually each day. Rescue medications as treatment for symptoms of allergic rhinoconjunctivitis will be provided with instructions for their use. Patients will score their rhinoconjunctivitis symptoms and rescue medication use in an electronic diary (e-diary) daily for 5 weeks.

Treatment Phase:

Visit 3 (Randomization Visit):
This Visit is to be performed within the 7 days following the 5-week run-in period. Patients with an average TCS ≥5/15 over the baseline evaluation period will be included in the treatment phase of the study. FEV_1 will be performed only on asthmatic patients. The patients will be randomized and assigned to one of the two treatment groups. Patients will be re-supplied with rescue medications as treatment for symptoms of allergic rhinoconjunctivitis if necessary, and reminded of instructions for their use. Patients will be asked to complete the RQLQ(S)≥12, EQ-5D-5L, and WPAI + CIQ: AS questionnaires prior to the first dose administration. The first dose of study treatment will be administered in the doctor's office and the patient will be monitored for at least 30 minutes thereafter.

During the treatment phase, patients will be scheduled for visits 1 month after randomization (Visit 4) and every 3 months thereafter (Visits 5 to 7).

In order to prevent missing data, patients who discontinued the treatment before the first interim evaluation period (i.e., before 3 months of treatment) will be asked to continue the study (without study treatment) until Visit 5 (i.e., until the end of the first interim evaluation period). Patients will be asked to score their rhinoconjunctivitis symptoms and rescue medication use on the e-diary during the first interim evaluation period.

Visit 4 (Month 1):
This Visit is to be performed 30 days ± 4 days after Visit 3. Treatment compliance and adverse event occurrence will be evaluated and recorded. Any potential issues or questions will be addressed. If necessary, additional training will be provided.

Visits 5 to 7 (Months 3, 6, and 9):
Visits 5, 6 and 7 are to be performed 90 days, 180 days and 270 days ± 7 days after Visit 3, respectively. Patients will be instructed to record their rhinoconjunctivitis symptoms and rescue medication use on the e-diary daily for a period of 2 weeks before each relevant visit scheduled after 3, 6 and 9 months of treatment. Patients will also evaluate the overall severity of the rhinitis symptoms on the VAS, on a weekly basis. Visits will be scheduled at the end of the 2-week evaluation period, or as close as possible thereafter.

Visit 8 (Month 11):
This Visit is to be performed 323 to 330 days after Visit 3. For patients who enter the study in late winter or spring (from February to June), this visit can be anticipated, but should not be earlier than 270 days after Visit 3. Patients will be instructed to start recording their rhinoconjunctivitis symptoms and rescue medication use daily using the e-diary and continue the daily recording for 4 weeks after this visit. This 4-week period will represent the primary evaluation period and should be performed one year later close to the 4 weeks of the baseline evaluation period. Over this 4-week period, patients will also evaluate the overall severity of the rhinitis symptoms on the VAS, on a weekly basis.

Visit 9 (Month 12):
This visit will be held at the end of the treatment period, 360 to 367 days after Visit 3. For patients who enter the study in late winter or spring (from February to June), this visit can be anticipated, but should not be earlier than 300 days after Visit 3. Patients will be questioned about any HDM avoidance measures implemented since the study start. RQLQ(S)≥12, EQ-5D-5L, Global Rating of Change Questionnaire, WPAI + CIQ: AS questionnaires, blood testing will be performed. FEV_1 will be performed only on asthmatic patients.

Post-treatment follow-up Phase:

Visit 10:
The post-treatment follow-up visit will be held 14 days ± 7 days after Visit 9.
Adverse events and use of concomitant medications will be recorded at all visits.

In the context of the study, a Data Safety Monitoring Board (DSMB) will regularly review cumulative safety data to monitor overall study safety.

Statistical methods:

Determination of Sample Size
The primary endpoint is the average TCS defined, for each patient, as the average of the non-missing daily TCSs over the last four weeks prior to the end of the treatment period.

[redacted] the clinical relevance of the efficacy results on the primary endpoint is pre-defined as follows [*Nelson et al.,2017*]:

- The relative difference of the TCS *versus* placebo should be ≤-15%, and
- The upper bound of the 95% CI of the TCS relative difference *versus* placebo should be ≤-10%

In the European study VO57.07 [*Bergmann et al., 2014*] conducted in 509 patients, the analysis of the average TCS showed a placebo mean of 3.65 and a relative mean difference of -17% between groups with a 95% CI of [-30% ; -3%]. The Coefficient of Variation (CV) was of 67% in the placebo group and 77% in the active group.

Based on this 95% CI (i.e., [-30% ; -3%]), an expected relative difference *versus* placebo of -20% was considered as a possible and reasonable value for the true relative difference between both groups. Besides, a CV of 75% was assumed to account for a possible higher variability of the data in this international study (i.e., North America, Europe, Israel and Russia).

Thus, assuming a two-sided nominal level of significance of 5%, a relative difference versus placebo of -20%, a placebo mean of 3.65, and a CV of 75%, simulations were performed based on 5,000 samples and showed that 739 evaluable patients per treatment group were sufficient to achieve a power of around 80% so as to fulfill both requirements (estimated relative difference versus placebo ≤-15% and upper bound of the 95% CI ≤-10%).

Of note, with the same assumptions and 739 evaluable patients per treatment group, the power of detecting a significant difference between both groups is greater than 99%.

Assuming a drop-out rate of 15% during the study, a total of 1,740 randomized patients (870 patients per group) will be required to ensure that 1,478 patients are included in the primary efficacy analysis. The screen failure rate is estimated at 50%, leading to a planned total number of screened patients of 3,480.

Determination of Study Populations for Analyses

Analysis Sets

- Safety Set:

The Safety Set will include all randomized patients who received at least one dose of the investigational product (IP).

All safety analyses will use the Safety Set.

- Full Analysis Set (FAS):

In order to be as close as possible to the Intent-To-Treat (ITT) principle, the Full Analysis Set will include all randomized patients who received at least one dose of the IP and have at least one primary efficacy evaluation during the treatment period (i.e., at least one day with a valid TCS during one of the evaluation periods).

The FAS will be the primary analysis set for all efficacy analyses (primary, secondary, [redacted]).

- Per Protocol Set (PPS):

The Per Protocol Set will include all patients in the FAS who complied with the study protocol without any major protocol deviations and had at least 14 days with a valid TCS during the primary evaluation period.

The primary efficacy analysis will be replicated in the PPS.

The definition of protocol deviations (minor or major) will be specified in the Statistical Analysis Plan (SAP). The classification of the protocol deviations as minor or major will be performed during the Data Review Meeting (DRM) before unblinding of the data.

Primary Efficacy Analysis:

The primary variable, the average TCS, will be summarized descriptively. The square root of the average TCS will be analyzed in the FAS during the primary evaluation period using an Analysis of Covariance (ANCOVA) with treatment group as main effect and pooled center, the square root of the baseline average TCS, age class (adolescent, adult), gender, asthma status (presence/absence) and sensitization status (mono-/poly-sensitized) as covariates.

Patients in the FAS having no efficacy evaluation during the primary period (i.e., no valid assessment) will not be part of the primary analysis. They will be included in the sensitivity analyses to assess the robustness of the primary analysis with regard to missing data. Sensitivity analyses will include Pattern-Mixture Models (PMMs) with reference-based imputation methods, a Mixed Model with Repeated Measures (MMRM) for the four evaluation periods and an analysis of the average TCS during the primary period using the Last Observation Carried Forward (LOCF) method.

The primary efficacy analysis will be repeated in the PPS as a supportive analysis.

The average TCS will also be analyzed in the FAS during the primary evaluation period using a Wilcoxon rank-sum test (non-parametric method). This analysis will be provided as a supportive analysis to check the consistency of results.

A point estimate and 95% Confidence Interval (CI) for the difference in means between the active treatment group and placebo will be calculated (primary analysis, sensitivity and supportive analyses). These results will also be expressed as relative difference (%) and relevant 95% CI compared to the placebo group.

Clinical Relevance of the Efficacy Results

[redacted] the clinical relevance of the results on the primary endpoint is pre-defined as follows [*Nelson et al.,2017*]:

- The relative difference of the TCS versus placebo should be ≤-15%, and
- The upper bound of the 95% confidence interval of the TCS relative difference versus placebo should be ≤-10%

Based on historical data obtained with STG320 in study VO57.07 [*Bergmann et al.,2014*], it is expected that the baseline average Total Combined Score (TCS) will be close to 7. Thus, a clinically meaningful effect of 15% in a given patient with an initial TCS of 7 would correspond to an improvement of about 1 point (15% of 7 is 1.08). More specifically, this threshold may be illustrated using e.g., the two following clinical cases:

- With an initial TCS of 7 and a constant RM intake, the patient will benefit from a symptom improvement of 1 point corresponding to a change of one severity class in one symptom e.g., from "severe" to "moderate"
- With an initial TCS of 7 and a stable symptom severity, the patient will experience a decrease of one step in RM intake e.g., s/he will stop the intranasal corticosteroids (from step 2: intranasal corticosteroids with or without antihistamine to step 1: antihistamine) or s/he will not take rescue medication anymore (from step 1: antihistamine to no rescue medication)

This clinical benefit is expected to last all year round as HDM allergic rhinitis induces perennial symptoms.

Secondary Efficacy Analyses:

Secondary efficacy analyses will be conducted in the FAS.
In order to control the overall type I error and to draw robust conclusions with regard to the key secondary endpoints, a step-down sequential closed testing procedure will be applied on six secondary endpoints which will be tested in the following order:

- 1. Rhinitis Total Symptom Score (RTSS) during the primary evaluation period

- 2. Overall score of Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at the end of the treatment period
- 3. Rhinoconjunctivitis Total Symptom Score (RCTSS) during the primary evaluation period
- 4. Blocked nose symptom score during the primary evaluation period
- 5. Proportion of Symptom-Controlled Days (PSCD, proportion of days with RTSS≤2 and no rescue medication use) during the primary evaluation period
- 6. Rescue Medication Score (RMS) during the primary evaluation period

The average RTSS, RMS, ASS, CSMS, TOSS, RCTSS and each of the six average individual RSSs (calculated as the average of the non-missing daily scores) during the primary evaluation period will be analyzed similarly to the average TCS using the corresponding baseline scores (except PPS analysis and sensitivity analyses). They will be summarized descriptively during each evaluation period.

The proportions of days with rescue medication intake will be summarized descriptively, overall and for each rescue medication category, and analyzed using a Wilcoxon rank-sum test at each evaluation period.

The $PSCD_{2\text{-}0}$ and PNCD will be summarized descriptively and analyzed using a Wilcoxon rank-sum test at the end of the treatment.

The $CP75_{2\text{-}0}$ will be summarized descriptively and analyzed using a χ^2 test at the end of the treatment.

The average VAS score (calculated as the average of the non-missing weekly scores), the overall RQLQ(S)≥12 score and RQLQ(S)≥12 scores by domain will be analyzed similarly to the primary efficacy variable using the corresponding baseline scores (except PPS analysis and sensitivity analyses).

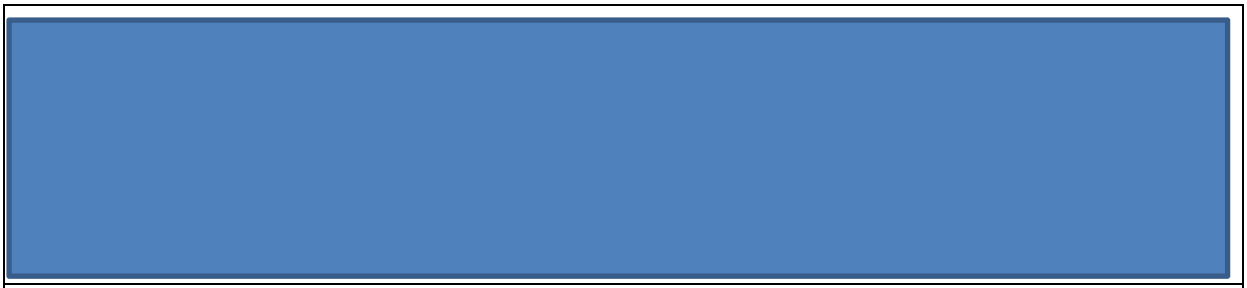
The EQ-5D-5L health profile (5 questions) and EQ-5D-5L VAS score will be summarized descriptively.

The GRCS will be analyzed by means of a Cochran Mantel-Haenszel test (row mean score statistic) using pooled centers as a stratification variable. The proportions of improved patients will be compared between groups using a χ^2 test or Fisher exact test.

Other analyses

The WPAI + CIQ: AS scores will be summarized descriptively. Percentage of impairment for each score will be calculated and described.

Immunological markers (*D. pte*- and *D. far*-specific serum IgE and IgG_4) before and after treatment as well as the fold-changes (i.e., the ratio after treatment to before treatment) will be summarized descriptively.



Safety Analyses

Safety data will be summarized in the Safety Set by treatment group using descriptive statistics: continuous variables by summary statistics and categorical variables by absolute and relative frequencies.

3.6 Flow Chart

Study Assessments	**Screening Phase**		**Treatment Phase**							**Post Treatment Follow-up Phase**
	Visit 1 Selection	**Visit 2 Run-in**	**Visit 3 Randomization = Visit 2 +5 weeks (+0 to 7 days)**	**Visit 4 1 mo FU = Visit 3 +30 days (±4 days)**	**Visit 5 3 mo FU = Visit 3 +90 days (±7 days)**	**Visit 6 6 mo FU = Visit 3 +180 days (±7 days)**	**Visit 7 9 mo FU = Visit 3 +270 days (±7 days)**	**Visit 8 11 mo FU = Visit 3 +323 to 330 days**	**Visit 9 12 mo FU = Visit 3 +360 to 367 days**	**Visit 10 2 wk post treat. = Visit 9 +14 days (±7 days)**
Informed consent	X									
Patient eligibility	X	X	X							
Medical history, demographics and Prior and Concomitant medication	X									
HDM avoidance measures questionnaire*									X	
FEV_1	X		X***						X***	
Physical examination (incl. vital signs)*	X								X	
Skin prick test (SPT)	X									
[redacted]										
Safety laboratory tests*	X								X	
Immunological markers (IgE, IgG_4) [redacted]*	X								X	
Pregnancy test (urine)	X		X							
Dispensing of placebo tablets for the run-in phase		X								
Randomization			X							
Dispensing of investigational product			X		X	X	X			
Dispensing of rescue medication		X	X	X	X	X	X	X		
Dispensing of epinephrine auto-injector			X							

Rhinoconjunctivitis Symptoms and Rescue medication use (e-diary) on a daily basis**		**X** **1+4 w**			**X** **2 w†**	**X** **2 w†**	**X** **2 w†**		**X** **4 w‡**	
VAS (e-diary) on a weekly basis**		**X**			**X**	**X**	**X**		**X**	
RQLQ(S)≥12*			**X**						**X**	
Global Rating of Change Questionnaires*									**X**	
WPAI + CIQ: AS and EQ-5D-5L Health Survey*			**X**						**X**	
Adverse events* and concomitant medication*		**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**

*: performed at Early Termination Visit in case of premature withdrawal; **: patients having discontinued the treatment before the first interim evaluation period will be asked to continue the study (without study treatment) and score their rhinoconjunctivitis symptoms and RM use until Visit 5 ***: FEV_1 only repeated on asthmatic patients at Visit 3 and at the end of study treatment or at early termination visit; †: patients will be asked to record their rhinoconjunctivitis symptoms and RM use for 2 weeks before Visit 5, Visit 6 and Visit 7; ‡: patients will be asked to record their rhinoconjunctivitis symptoms and RM use during the 4 weeks from Visit 8 to Visit 9.

Notes:

Immunological markers: Serum IgE and IgG_4 specific for *D. pte* and *D. far* allergens should be tested in patients with positive SPT at Visit 1. Testing should be repeated at Visit 9.

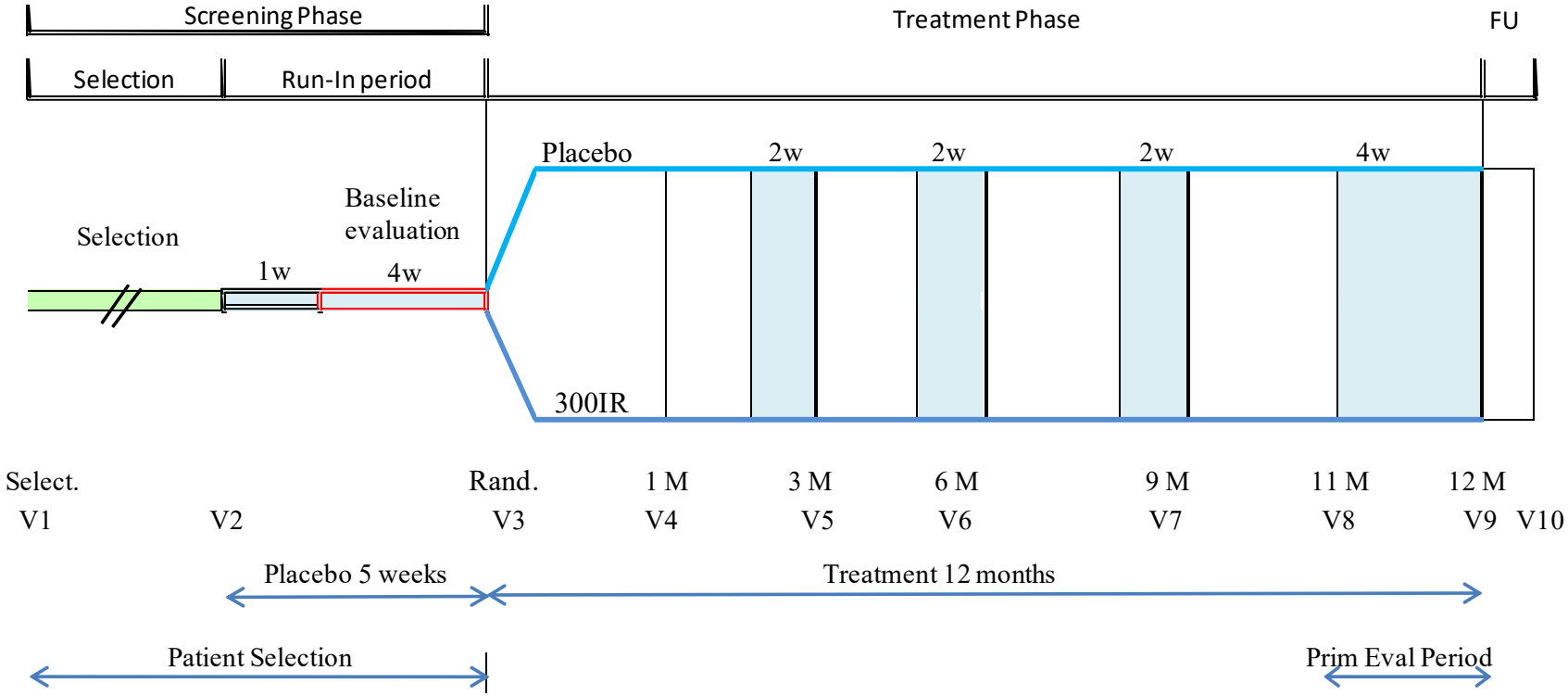
Safety Laboratory Tests: Hematology: hemoglobin, hematocrit, red blood cells (RBC), platelets, white blood cells (WBC), differential count (neutrophils, basophils, eosinophils, monocytes, lymphocytes) and Biochemistry: glucose, creatinine, sodium, potassium, chloride, bilirubin (direct, indirect, total), ASAT (SGOT), ALAT (SGPT), GGT, performed at Visits 1 and 9.

E-diary: An electronic diary (e-diary) will be dispensed to patients at Visit 2. Patients will be asked to bring back the device to the study site at each visit. Patient will assess rhinoconjunctivitis symptoms and rescue medication usage daily at the same time after awakening.

Epinephrine auto-injector: At Visit 3, patients will be supplied with an epinephrine auto-injector and they will be instructed when and how to use it. At each subsequent visit until Visit 9, the Investigator will check if the patient has used this device. If the previously dispensed device has been lost or used for an AE that does not require the patient's withdrawal from the study, a new auto-injector will be dispensed.

Visit 8 and Visit 9 dates: For patients who enter the study in late winter or spring (from February to June), Visit 8 and Visit 9 will be anticipated when needed, but should not be earlier than 270 and 300 days after Visit 3, respectively.

3.7 Study Schematic Diagram



3.8 List of Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
AIT	Allergen Immunotherapy
ALAT (SGPT)	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AR	Allergic Rhinitis
ASAT (SGOT)	Aspartate Aminotransferase
ASS	Adjusted Symptom Score
ATC	Anatomical Therapeutic Chemical
ATS/ERS	American Thoracic Society/European Respiratory Society
CI	Confidence Interval
CP	Controlled Patient
CPMP	Committee for Proprietary Medicinal Products
CRO	Contract Research Organization
CSMS	Combined Score and Medication Score
CV	Coefficient of Variation
D. far	*Dermatophagoides farinae*
D. pte	*Dermatophagoides pteronyssinus*
DRM	Data Review Meeting
DSMB	Data Safety Monitoring Board
e-CRF	Electronic Case Report Form
e-diary	Electronic Diary
EGD	Esophagogastroduodenoscopy
EoE	Eosinophilic Esophagitis
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume in one second
GCP	Good Clinical Practice

GGT	Gamma Glutamyl Transferase
GINA	Global Initiative for Asthma
GP	General Practitioner
GRCS	Global Rating of Change Score
HDM	House Dust Mites
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
ICU	Intensive Care Unit
Ig	Immunoglobulin
IP	Investigational Product
IR	Index of Reactivity
ITT	Intention-To-Treat
IVRS/IWRS	Interactive Voice/Web Response System
LABA	Long-Acting Beta(ß)2-Agonist
LS	Least Square
LOCF	Last Observation Carried Forward
MAOI	Monoamine Oxidase Inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
MMRM	Mixed Model with Repeated Measures
PMM	Pattern Mixture Model
PNCD	Proportion of Not-Controlled Days
PPS	Per Protocol Set
PSCD	Proportion of Symptom-Controlled Day
PT	Preferred Term
RBC	Red Blood Cells
RCTSS	Rhinoconjunctivitis Total Symptom Score
RM	Rescue Medication
RMS	Rescue Medication Score

RQLQ(S)≥12	Standardized Rhinoconjunctivitis Quality of Life Questionnaire for Subjects ≥12 Years of Age
RSS	Rhinoconjunctivitis Symptom Score
RTSS	Rhinitis Total Symptom Score
SABA	Short-Acting Beta(ß)$_2$-Agonist
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCIT	Subcutaneous Immunotherapy
SD	Standard Deviation
SLIT	Sublingual Immunotherapy
SOC	System Organ Class
SOP	Standard Operating Procedure
SPT	Skin Prick Test
TCS	Total Combined Score
TEAE	Treatment-Emergent Adverse Event
TMF	Trial Master File
TOSS	Total Ocular Symptom Score
USA	United States of America
VAS	Visual Analog Scale
WBC	White Blood Cell
WPAI + CIQ: AS	Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific

4. BACKGROUND INFORMATION

4.1 Scientific Background

Allergy is one of the most common diseases in the world. Untreated or inadequately treated Allergy Rhinitis (AR) can cause sleep disturbance, daytime fatigue and somnolence [*Leger et al.,2006*] as well as depressed mood, irritability, behavioral problems [*Meltzer,2001; Hankin et al.,2010*] or impaired social functioning [*Meltzer,2001*]. There are also significant indirect costs associated with this condition including absenteeism from work or school and decreased productivity when at work [*Blaiss,2007*].

Using a conservative estimate, AR occurs in over 500 million people around the world [*Bousquet et al.,2008*]. Sneezing, congestion, clear rhinorrhoea and nasal pruritus are the key symptoms characterizing the disease. It is estimated that AR affects up to 60 million people in the United States (US), and its prevalence is increasing. Despite a reported prevalence ranging from 10 to 30% in adults and up to 40% in children [*Warner et al.,2006*], AR is frequently under-recognized, misdiagnosed, and ineffectively treated [*Meltzer et al.,2012*]. The prevalence peaks in childhood and adolescence and decreases in the elderly. It has been established that the pathophysiogical mechanisms of rhinitis contribute to the development of asthma in a large number of patients [*Rowe-Jones,1997*]. The risk for AR patients in developing asthma is three times higher than among the general population (10% versus 3.6%), confirming the hypothesis that rhinitis is often the first step in the natural history of asthma [*Rachelefsky,1999*].

Allergens such as cat and dog dander, cockroach and house dust mite are associated with perennial rhinitis while allergies to grass, weeds, and tree pollens are characterized by seasonal rhinitis symptoms.

Mites consist of a large taxonomic subclass, named Acarina. Among them, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* are the main species involved in AR in Europe and North America [*Platts-Mills and Weck,1989*].The most important habitat for *Dermatophagoides* mites is in bedding (mattress and bed clothes), where the food is supplied as human scales and where the temperature is ideal. Overstuffed furniture, carpets and unlaundered clothing are also important habitats [*Mosbech,1985*].

Current treatment options are allergen avoidance, symptomatic therapy, and specific immunotherapy. Allergen avoidance is often virtually impossible. Symptomatic treatments include antihistamines, intranasal corticosteroids, chromones and leukotriene modifiers. These treatments provide temporary relief from allergy symptoms but are not effective in all patients and do not have a disease-modifying effect [*Nathan,2007*]. In addition, pharmacotherapy may be associated with significant side effects such as sedative and anticholinergic effects for antihistamines, dryness and epistaxis for intranasal corticosteroids and neuropsychiatric reactions for leukotriene modifiers [*Byrne et al.,2012; Fernández-Caldas,2013*].

Allergen immunotherapy is the only therapy available that acts on the main cause of the allergic reaction by modifying or down-regulating the immune response to allergens.

Allergen-specific subcutaneous immunotherapy (SCIT) is the oldest route of administration used to desensitize patients and is still a recommended therapeutic option for subjects with AR [*Cox et al.,2011*]. However, despite its long use history, only 5% of the US population with AR, asthma, or both benefit from this treatment [*Cox,2008*]. Its use is limited by the risk of near-fatal or fatal anaphylaxis as well as the discomfort and inconvenience of frequent injections [*Bernstein et al.,2004; Amin et al.,2006; Nelson,2007*].

Allergen-specific sublingual immunotherapy (SLIT) is an alternative to SCIT with similar efficacy [*Canonica et al.,2009; Cox et al.,2011; Canonica et al.,2014*]. The favorable safety profile of SLIT and its convenience are likely factors for the substantial and growing increase in its use [*Nelson,2007; Cox and Jacobsen,2009*]. The Allergic Rhinitis and its Impact on Asthma (ARIA) 2008 Update [*Bousquet et al.,2008*] and its 2010 revision [*Brozek et al.,2010*] provide recent expert guidance in this therapeutic area. These reviews indicate that SLIT may be used for the treatment of subjects with mite allergy. In addition, recent Cochrane reviews [*Radulovic et al.,2010; Lin et al.,2013*] confirm that SLIT is a viable alternative to SCIT with a significantly lower risk profile and little difference in overall efficacy.

STALLERGENES is developing a sublingual immunotherapy (SLIT) tablet of HDM allergen extracts (STG320 HDM sublingual tablets) containing standardized allergen extracts from both *Dermatophagoides pteronyssinus (D. pte)* and *Dermatophagoides farinae (D. far)*. The efficacy and safety of STG320 tablets at daily doses of 300IR and 500IR have been demonstrated in adults and adolescents with AR.

The purpose of the present study is to confirm the efficacy and safety of STG320 sublingual tablets at the daily dose of 300IR in adults and adolescents with HDM-associated AR.

4.2 Investigational Product

The Investigational Product (IP) is STG320 HDM sublingual tablet containing extracts of *Dermatophagoides pteronyssinus* (*D. pte*) and *Dermatophagoides farinae* (*D. far*) [active substance].

STG320 is obtained by extracting, purifiying, freeze-drying and sieving of the genuine allergen sources. These drug substances are obtained separately from both *D. pte* and *D. far* and then mixed together in a 50:50 immunological activity ratio (expressed in IR). The mixture is processed by direct compression to obtain the sublingual tablets of HDM allergen extracts.

The allergen preparation potency unit used by STALLERGENES is defined as Index of Reactivity or "IR" [*Hrabina et al.,2007; Wahn et al.,2009*]. The titer of an allergen extract corresponds to 100 IR/mL when, in a skin prick test performed with the STALLERGENES skin prick test device (i.e., the Stallerpoint®), in 30 subjects sensitized to the allergen in question, the extract produces a wheal measuring 7 mm in diameter (geometric mean). Skin reactivity in these subjects is simultaneously demonstrated by a positive response to a prick-test with 9% codeine phosphate or 10 mg/mL histamine dihydrochloride.

The IP is further described in *Section 8.1* "Study Investigational Products" and in the Investigator's Brochure (Version 10 dated 11 June 2014).

4.3 Non-Clinical Studies

Detailed information on the non-clinical experience with STG320 can be found in the Investigator's Brochure. A summary of this information is provided below.

4.3.1 Pharmacology

Published animal studies demonstrate the alleviation or prevention of type-I hypersensitivity reactions upon allergen re-challenge of sensitized animals following repeated administration of allergens. To strengthen these experimental results and to extend them to the mite extracts manufactured at STALLERGENES, freeze-dried extracts of *D. pte*/*D. far* were tested in a murine model of chronic HDM-induced asthma. The study results demonstrated that the freeze-dried extracts of *D. pte/D. far* are efficacious as a sublingual immunotherapy vaccine in the murine model [Study DS/ST/09/234 – refer to the STG320 Investigator Brochure].

4.3.2 Pharmacokinetics

No animal pharmacokinetics data have been generated with the mite extracts. The lack of relevance of pharmacokinetic data can be explained as follows:

- By the sublingual-swallow route, the proteolytic digestion in the gastrointestinal tract is assumed to be the predominant fate of mite extracts, as they consist mostly of proteins and glycoproteins. The extent of systemic absorption of the mite extracts is unknown but is assumed to be negligible.
- Based on our knowledge of the mechanism of action of SLIT, the pharmacological effect of the mite extracts included in the tablets is not related to plasma allergen levels but to the capture of allergens by dendritic cells within the sublingual mucosa and transport to draining lymph nodes.

4.3.3 Toxicology

Repeat-dose oral (gavage) and subcutaneous administration of freeze-dried extracts of *D. pte* and *D. far* in rats were well tolerated. No evidence of treatment-related toxicity was noted after doses of up to 2,500 IR/kg/day administered for 26 weeks.

4.4 Clinical Development

STALLERGENES is conducting a multinational clinical development program with STG320 for the treatment of HDM-associated AR. To date, seven clinical studies evaluating the sublingual tablet for this indication have been conducted: five by STALLERGENES and two by Shionogi & Co., Ltd.

4.4.1 STALLERGENES - Sponsored Studies

Studies in Adults

- **Phase I Study VO36.04F in adults [aged 18 to 50 years]**

This phase I, randomized, double-blind, placebo-controlled single-center study in 31 adults (18-50 years old) with perennial AR caused by sensitization to house-dust mites assessed the safety and tolerability of four STG320 dose regimens with 10 days of administration: two incremental dose regimens up to 500 IR and constant dose regimens at 500 IR or 300 IR.

STG320 was generally well tolerated at doses up to 500 IR. It was concluded that a dose escalation period could reduce the incidence and severity of application site reactions.

- **Phase II/III Study VO57.07 in adults [aged 18 to 50 years]**

This natural field, randomized, double-blind, placebo-controlled, multi-center study was conducted in adults with HDM-related AR to assess the efficacy and safety of STG320 at the 300 IR and 500 IR doses. The study included a 12 month treatment period (Year 1) and a 12 month treatment free follow-up period (Year 2). 509 patients were enrolled, 427 completed the first year, and 397 completed the second year. Statistically significant differences between the 300 IR group and the 500 IR group compared to placebo on the primary endpoint were demonstrated during the Year 1 primary evaluation period. The difference between the two active treatment groups was not statistically significant. Efficacy was maintained during the treatment-free follow-up year (Year 2). The overall safety profile of the two doses was favorable with no appreciable differences in tolerability between them. No anaphylaxis or autoimmune disorders were reported. No unexpected risk was identified [*Bergmann et al.,2014*].

- **Phase II Study VO67.10 Environmental Exposure Chamber in adults [aged 18 to 55 years]**

This randomized, double-blind, placebo-controlled, multi-center, dose ranging study, performed in an Environmental Exposure Chamber, was conducted in Canada in 355 adults with HDM-related AR. It evaluated the efficacy, safety and tolerability of 100 IR, 300 IR and 500 IR administered once daily for 6 months. A dose effect was observed on the primary efficacy endpoint. The reduction in symptom severity was limited with the 100 IR dose (19.8%), but larger with the 300 IR (28.8%) and the 500 IR doses (33.2%). The overall safety profile was consistent with that observed in previous studies.

Studies in Children and Adolescents

- **Phase III Study VO64.08 in children and adolescents [aged 5 to 17 years]**

This natural field, randomized, double-blind, placebo-controlled, multi-center study was conducted in Europe in children and adolescents with HDM-associated AR to assess the safety and efficacy of STG320 at the 300 IR dose. Overall, 471 patients (241 in the 300 IR group and 230 in the placebo group) were randomized.

This study was initially designed to include 24 months of treatment (i.e., 12 months of treatment in Year 1 and 6 months of treatment in each of Year 2 and Year 3) and 22 months of treatment-free

follow-up. While all patients met the study inclusion criteria (i.e., clinical history, positive prick skin test, positive HDM-specific serum IgE, and the presence of symptoms at baseline), they reported minimal symptoms post-randomization. Therefore, the efficacy of the investigational product could not be assessed. Accordingly, the Data Safety Monitoring Board of independent external experts recommended the early termination of the study "for futility", before the patients started the second treatment period. These findings underscore the need for additional diagnostic criteria in future pediatric studies to ensure the enrollment of patients with HDM-driven AR.

The safety profile of the 300 IR dose of STG320 in children and adolescents was consistent with that observed in previous studies in adults. Patients with asthma showed a similar safety profile as those without asthma.

- **Phase I Study VO73.13 in adolescents [aged 12 to 17 years]**

This randomized, double-blind, placebo-controlled, single-center study (Canada) assessed the safety and tolerability of 3 dose-regimens, 500 IR, 1000 IR and 1500 IR of STG320 sublingual tablets evaluated over a treatment period of 10 consecutive days in 37 adolescents with HDM-associated AR. The three doses were well tolerated. The overall safety profile was consistent with that observed in previous studies with the 300 IR and 500 IR doses in adults, adolescents and children.

4.4.2 Studies Conducted by STALLERGENES Partner Company (Shionogi and Co., Ltd)

- **Phase I Study 1109D1711 in adults [aged 20 to 39 years]**

This randomized, double-blind, placebo-controlled, single-center study (Japan) assessed the safety of three doses (100 IR, 300 IR and 500 IR) of STG320 *versus* placebo in 36 adults with HDM-associated perennial allergic rhinitis treated for 14 days. All doses were well tolerated.

- **Phase II/III Study 1207D1731 in adolescents and adults [aged 12 to 64 years]**

This natural field, randomized, double-blind, placebo-controlled, multi-center (Japan) study was conducted in adolescents and adults with HDM-related AR to assess the efficacy and safety of STG320 at the doses of 300 IR and 500 IR over a 12 month treatment period.

968 patients (181 adolescents) were enrolled and 853 patients (159 adolescents) completed the 12-month treatment phase. Statistically significant differences between both the 500 IR group and the 300 IR group compared to placebo on the primary endpoint were demonstrated. A subgroup analysis in adolescents (age category: ≥12 to <18) showed statistically significant differences between both 500 IR and 300 IR compared to placebo on the primary efficacy endpoint.

The safety profile was consistent with that observed in studies conducted in Europe and Canada.

4.5 Study Rationale

Up to 09 June 2015, 1,571 patients (1,182 adults, 261 adolescents and 128 children) with HDM-associated AR have been exposed to STG320 (doses from 100 IR to 1500 IR) in the rhinitis development program.

Overall, the results of the natural field and environmental exposure chamber studies demonstrate that the 500 IR and 300 IR doses of STG320 are similarly efficacious in treating adults with HDM-induced AR.

A favorable safety and tolerability profile has been observed for all tested doses. No deaths were reported. There were no reports of anaphylactic shock, anaphylaxis, or Intensive Care Unit (ICU) admission and no use of epinephrine. The most frequent adverse reactions were application site reactions such as oral pruritus and throat irritation. Most were of mild or moderate intensity and were mainly reported during the first weeks of treatment. Drug-related adverse events (AEs) leading to premature discontinuation were more frequent in active treatment groups compared to placebo.

Based on the totality of the efficacy and safety data, the development of the 300 IR dose of STG320 will be pursued.

This randomized, double-blind, placebo-controlled study is designed to confirm the efficacy and safety of the 300 IR dose of STG320 in adolescents and adults (12-65 years of age) with HDM-associated AR. Treatment will be administered daily for 12 months. Patients will be selected on the basis of a clinical history consistent with HDM-associated AR, positive skin prick test and the presence of HDM-specific serum IgE. To better enable the identification of patients whose symptoms are driven by HDM allergy, evidence of HDM-exposure has been added as an inclusion criterion.

4.6 Good Clinical Practices Statement

The present study will be conducted in accordance with:

- This protocol
- International Conference on Harmonization: ICH E6 Note for Guidance on Good Clinical Practice [CPMP/ICH/135/95]
- International Conference on Harmonization: ICH E11 Clinical Investigation of Medicinal Products in the Paediatric Population [CPMP/ICH/2711/99]
- Code of Federal Regulations on Good Clinical Practice, Title 21 – Parts 50, 54, 56, 312, 314) and
- The principles that have their origin in the Declaration of Helsinki
- Applicable local laws and regulations

5. STUDY OBJECTIVES AND PURPOSE

This study is designed to assess the efficacy and safety of 12 months of treatment with 300 IR of STG320 sublingual tablets compared with placebo in adults and adolescents with house dust mite (HDM)-associated allergic rhinitis (AR).

5.1 Primary Objective

The primary objective of this study is to evaluate the efficacy of STG320 sublingual tablets at a daily dosage of 300 IR when administered for 12 months to adults and adolescents with HDM-associated AR.

The primary efficacy variable will be the average Total Combined Score (TCS), calculated for each patient as the average of the non-missing daily TCSs during the primary evaluation period (i.e., the last 4 weeks of treatment). The daily TCS (scale 0-15) is the sum of the patient's daily Rhinitis Total Symptom Score (RTSS, scale 0-12) and daily Rescue Medication Score (RMS, scale 0-3).

5.2 Secondary Objectives

5.2.1 Efficacy of STG320 during the Primary Evaluation Period (Month 12)

To assess the efficacy of STG320 sublingual tablets at the dosage of 300 IR as evaluated by the following secondary efficacy variables during the primary evaluation period

- Rhinitis Total Symptom Score (RTSS).
- Rescue Medication Score (RMS)
- Adjusted Symptom Score (ASS, scale 0-12). This score is derived from the daily RTSSs, after adjustment for the patient's rescue medication use.
- Combined Symptom and Medication Score (CSMS, scale 0-6). The CSMS is derived from RTSS and RMS.
- Total Ocular Symptom Score (TOSS, scale 0-6). The TOSS is calculated as the sum of individual scores for itchy/red eyes and watery eyes.
- Rhinoconjunctivitis Total Symptom Score (RCTSS). The RCTSS is calculated as the sum of the four rhinitis symptom scores and the two ocular symptom scores.
- Each of the six individual Rhinoconjunctivitis Symptom Scores (RSSs, each scored on a scale of 0-3): itchy nose, sneezing, runny nose, blocked nose, itchy/red eyes and watery eyes.
- Rhinoconjunctivitis rescue medication use, overall and by type of treatment.
- Visual Analogue Scale (VAS) assessing the intensity of the allergic rhinitis symptoms (ranging from 0 = absence of symptoms to 100 = very severe symptoms).

- Proportion of Symptom-controlled Days (PSCD), Proportion of Not-Controlled Days (PNCD) and Controlled Patients (CP)
- Overall Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)≥12) and RQLQ(S)≥12 domains.
- Health questionnaire EQ-5D-5L
- Global Rating of Change Score (GRCS) (15-point Likert scale)

5.2.2 Efficacy of STG320 during the Secondary Evaluation Periods (Months 3, 6 and 9)

Rhinoconjunctivitis symptom evaluation and rescue medication use will also be evaluated during the 2-week secondary evaluation periods (i.e., assessment to be started 2 weeks before the relevant visits at Month 3, Month 6 and Month 9). The following endpoints will be assessed:

- TCS
- RTSS
- RMS
- ASS
- CSMS
- TOSS
- RCTSS
- RSSs
- Rhinoconjunctivitis rescue medication use, overall and by type of treatment
- Overall assessment of allergic rhinitis symptoms by a Visual Analogue Scale (VAS)

5.2.3 Effect of STG320 at the End of the Treatment

To assess the effect of STG320 compared to placebo on other variables at the end of the treatment

- Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI + CIQ: AS)
- Immunological markers: *D. pte*- and *D. far*-specific serum IgE and IgG_4

[redacted]

5.4 Safety Objectives

To assess the safety of 12 months of treatment with STG320 at the daily dose of 300 IR. The safety assessments include adverse events (AEs), Adverse Events of Special Interest (AESI) (anaphylaxis, severe laryngopharyngeal disorders, autoimmune disorders and eosinophilic esophagitis), vital signs and routine safety laboratory tests.

6. STUDY DESIGN

6.1 Type/Design

This is a randomized, double-blind, placebo-controlled, phase III study with two parallel arms to be conducted in patients with HDM-associated allergic rhinitis consisting of a 1 to 6 month screening phase (including a run-in period of 5 weeks), a treatment phase of approximately 12 months and post-treatment follow-up phase of 2 weeks.

Male or female patients aged 12 to 65 years (inclusive) with HDM-related allergic rhinitis for at least one year requiring regular intake of symptomatic treatments will be randomized to one of two treatment groups.

In addition to the patients' history, the diagnosis will be confirmed by the positivity of Skin Prick Test (SPT) with HDM allergen and the presence of HDM-specific IgE. [redacted]

Overall, each patient is to attend 10 visits. Visits 1 will involve screening for eligibility. Visit 2 will start the run-in phase. Visit 3 to Visit 9 will comprise the treatment phase and Visit 10 will involve the post-treatment follow-up phase.

Screening Phase (Visit 1 and Visit 2)

- **Selection Visit (Visit 1)**

At Visit 1, the first screen will be performed to assess patient's eligibility for the study.

- **Run-in period (Visit 2)**

At Visit 2, patients still meeting all of the inclusion and none of the exclusion criteria, except the criteria assessed on the baseline TCS, will enter a single-blind placebo run-in period of 5 weeks. The selected period will be individualized based on the patient's history of previous HDM-related rhinitis symptoms (i.e., the period during which the patient is reported to be the most symptomatic). During this period, patients will take 1 placebo tablet sublingually each day. Rescue medications as treatment for symptoms of allergic rhinitis to HDM will be provided with instructions for their use. Patients will record their rhinoconjunctivitis symptoms and rescue medication use in an electronic diary (e-diary) daily and will assess the intensity of the AR symptoms on a Visual Analogue Scale (VAS) weekly for 5 weeks.

An average TCS ≥5 (scale 0 to 15) during the four last weeks of the run-in period will serve as an ultimate inclusion criterion for the selection of patients for randomization.

For those patients who meet this inclusion criterion, these 4 weeks will also serve as the baseline evaluation period.

Treatment Phase (Visits 3-9)

At Visit 3, eligible patients will be randomized 1:1 to either active treatment or placebo. The first dose of study treatment will be administered at the study site and the patient will be monitored for at least 30 minutes thereafter. Subsequent doses are to be taken at home, daily, at the same time in the morning, for a period of approximately 12 months with a minimum of 10 months. Interim efficacy assessments will be performed at Month 3, 6, and 9 after randomization (Visits 5-7). The primary efficacy evaluation period (from Visit 8 to Visit 9) will be during the same 4 weeks of the year as those of the baseline evaluation period or as close as possible to these weeks.

A limited shortening of the 12-month treatment phase should be considered when necessary in patients who enter the study in late winter or spring (from February to June), in order to adapt and to avoid possibly less favorable conditions for mite exposure in late winter/spring and to prevent confounding symptoms due to pollens in case of early pollination in the following year. The purpose of this relative flexibility in planning the treatment duration for those patients is to ensure the primary efficacy evaluation is performed when conditions are optimal for such evaluation.

Post-Treatment Follow-Up Phase (Visit 10)

Patients will attend a follow-up visit, 2 weeks after the administration of their last IP dose.

6.2 Number of Patients and Study Sites

It is planned to screen approximately 3,500 patients in order to randomize 1,740 (i.e., 870 patients randomized in each treatment group). Approximately 150-190 centers from the United States of America (USA), Canada, Europe, Israel and Russia are expected to participate.

6.3 Measures to Minimize Bias

6.3.1 Randomization

All patients will receive a screening number via an Interactive Web/Voice Response System (IVRS/IWRS).

A computer-generated randomization list with stratification by study site will be prepared by a different statistician from the biostatisticians in charge of the study data analyses.

A copy of the complete randomization list will be provided to the IVRS/IWRS responsible person and to the company contracted to package the investigational product.

6.3.2 Blinding

During the run-in period, patients will receive placebo tablets. All efforts are to be taken by study site personnel to not reveal to the patients the placebo nature of the tablets and maintain the single blind.

After randomization and throughout the study treatment and post-treatment phases, the study is designed as a double-blind study. Therefore, during the treatment phase, patients, investigators and site staff, and all study staff will be blinded as to treatment group assignment. The investigational products (i.e., active and placebo tablets) will be the same with respect to appearance and taste. Labeling and packaging will also be identical.

Under normal circumstances, the treatment blind must be maintained. In the case of medical emergency in which knowledge of the treatment allocation is considered by the Investigator as critical in managing the patient's condition, the Investigator will utilize IVRS/IWRS and use the unblinding functions. In case of technical issues with the IVRS/IWRS system, the Investigator will contact either the responsible person from the Pharmacovigilance department or the primary CRO designee to unblind the patient.

If the blind is broken, the date, the reason for breaking the blind, and the person doing so is to be recorded on the source document, and in the appropriate e-CRF page, and STALLERGENES or its representative must be notified immediately.

6.4 Study Duration

The total duration of the study for an individual patient will be between 14 and 20 months, including a 1- to 6-month screening phase (including a run-in period of 5 weeks), a treatment phase of 12 months and a post-treatment follow-up phase of 2 weeks.

In total, 10 visits will be conducted: 2 screening visits, 1 randomization visit, 6 regular follow-up visits (Months 1, 3, 6, 9, 11 and 12) and 1 post-treatment visit (Month 12.5).

Evaluation periods

The evaluation periods will be defined as follows:

- Baseline evaluation period: last 4 weeks of the 5-week run-in period
- Interim evaluation periods: 2 weeks every 3 months after randomization (i.e., Month 3, Month 6 and Month 9)
- Primary evaluation period: 4 weeks prior to the end of the treatment period

7. SELECTION AND WITHDRAWAL OF PATIENTS

Before any study procedures are initiated for any patient in this study, approval of the Institutional Review Board (IRB) or Ethics Committee will have to be obtained, and written informed consent, including signing of the informed consent/assent form, must be documented.

7.1 Inclusion Criteria

The patient must fulfill the following inclusion criteria to be eligible for the study

1. Have house dust mite (HDM)-associated allergic rhinitis (AR) (with or without asthma) for at least 1 year based on the presence of:

- Symptoms for 4 or more consecutive weeks in the previous year and for at least 4 days per week during those weeks.
- Symptoms requiring regular intake of symptomatic treatment(s).
- Symptoms evaluated as "troublesome" by the patients or impairing their daily activities, leisure or sport, school or work or involving sleep disturbance.

2. Have given signed informed consent to participate, after having been informed of the nature and aims of the study, in accordance with local regulation and requirements.
3. Male or female outpatients 12 to 65 years of age.
4. Sensitized to *D. pteronyssinus (D. pte)* and/or *D. farinae (D. far)* defined as skin prick test wheal diameter at least 5 mm greater than the negative control and HDM-specific serum IgE ≥3.5 kU/L.
5. Willing to and capable of completing the e-diary, study questionnaires and scales.

7.2 Exclusion Criteria

If a patient meets any of the following criteria, s/he cannot participate in this study:

1. A history of rhinitis, rhino-conjunctivitis or asthma to allergens other than HDM, likely to result in rhinitis symptoms during the baseline and primary evaluation periods.

   Specifically, when the following are present:

   - documented sensitization (positive Skin Prick Test [wheal diameter at least 5 mm greater than the negative control] or allergen specific serum IgE ≥3.5kU/L) and history of clinically relevant symptoms to allergen(s) other than HDM
   - anticipated exposure to such allergen(s) during the baseline and primary evaluation periods

   For example, the following patients are to be excluded:

   - patients sensitized to cat or dog allergens and regularly exposed to these animals
   - patients sensitized to perennial allergens, such as aspergillus, cladosporium, alternaria, cockroach
   - patients sensitized to seasonal allergens such as parietaria, ragweed or mugwort, if these allergens are endemic in the region during the baseline and primary evaluation periods.

2. Any diagnosed nasal (other than HDM allergic rhinitis) or oral disease that could interfere with the efficacy or safety assessments, such as nasal polyposis, recurrent chronic rhino-sinusitis (at least 2 isolated episodes per year in the 2 previous years, each episode lasting more than 8 weeks) or a history of chronic oral inflammation or current active oral inflammation from any etiology (e.g., oral lichen planus, oral ulceration or oral mycosis) and/or oral wounds.
3. Recent nasal surgery (i.e., within the previous 6 months).

4. Partly controlled or uncontrolled asthma defined in the Global Initiative for Asthma 2014 guidelines (GINA 2014) as the presence of daytime asthma symptoms more than twice/week or nocturnal symptoms/awakening or need for reliever/rescue treatment more than twice/week or FEV_1 <80% of predicted or personal best value.
5. Asthma therapies consistent with GINA treatment Step 3, Step 4 and Step 5 i.e., the preferred controller medication consists of inhaled corticosteroid (ICS) combined with long-acting beta (β)-2 agonist (LABA) according to GINA classification 2014 (refer to *Appendix II* for the full details of other controller options).

   Eligible asthmatic patients will be those with asthma, controlled by treatment(s) consistent with GINA 2014 treatment Steps 1 or 2 [i.e., reliever treatment with as needed short acting β2-agonist with or without controller treatment consisting of low dose inhaled corticosteroid (i.e., ≤400 µg of budesonide/day or equivalent dose of other corticosteroid) or leukotriene receptor antagonist or low dose theophylline].
6. Experienced a life-threatening asthma attack or an asthma exacerbation that resulted in Intensive Care Unit (ICU) hospitalization.
7. Requiring continuous treatment with systemic corticosteroids for any indication.
8. Requiring continuous treatment with β-blockers or with Monoamine Oxidase Inhibitors (MAOIs).
9. Received an immunosuppressive treatment within 3 months prior to screening.
10. Received allergen immunotherapy (AIT) by any route:
    - for house dust mites: AIT for more than 1 month within the 5 years before screening
    - for other allergen(s): ongoing or recently stopped (within 6 months) AIT.
11. Any history of anaphylaxis after previous allergen immunotherapy, exposure to allergen(s) or of unknown cause.
12. A history of hypersensitivity to STG320 or its excipients or contraindication to the use of rescue medications (i.e., antihistamines and corticosteroids).
13. Female with positive urine pregnancy test or lactating or expecting to conceive within the duration of the study.
14. Sexually active female of child-bearing potential without medically accepted contraceptive method: hormonal birth control (orally, injectable or by implant, for at least 2 months before enrollment), intrauterine device, male condom or diaphragm used with spermicide, monogamous relationship with a vasectomised partner. Women are considered not to have childbearing potential prior to menarche or at least 2 years after menopause or if they have had a bilateral tubal ligation or a total hysterectomy or bilateral oophorectomy or ovariectomy.
15. Unable or unwilling to comply with the study protocol requirements, including those who anticipate significant changes in their daily environment in relation to HDM exposure or

who are likely to travel for extended periods of time during the main efficacy assessment period.

16. Patients with past or current disease(s) which, as judged by the Investigator, may affect the patient's participation in or the outcome of this study. These diseases include, but are not limited to, cardiovascular disease, malignancy, active tuberculosis, hepatic disease, renal disease, hematologic disease, neurologic or psychiatric disease, severe autoimmune disorder, immunodeficiency or immunologic disease and endocrine disease.
17. Patients with a history of eosinophilic esophagitis or with current severe or persistent gastroesophageal symptoms including dysphagia or chest pain.
18. Contraindications to allergen specific immunotherapy.
19. Patients with history of drug or alcohol abuse.
20. Participation in any clinical study within 30 days prior to the selection visit.
21. Possible dependency of the patient on sponsor or investigators/subinvestigators or study personnel.

Patients who fulfill all of the above inclusion criteria and none of the exclusion criteria will be eligible for the 5-week placebo run-in period. During this period, patients will take placebo tablets (single-blind) and will score their HDM-associated allergic rhinoconjunctivitis symptoms and record rescue medication usage on a daily basis. The last 4 weeks will be used as the baseline evaluation period.

7.3 Inclusion Criterion at the end of the run-in/baseline evaluation period

Only patients who fulfill the following criterion will be eligible for randomization:

- Patients with an average TCS ≥5 (on a scale of 0 to 15) over the baseline evaluation period.

7.4 Patient Withdrawal

In case of patient withdrawal or early discontinuation, the Investigator should make every effort to complete the final evaluation as stipulated in the *Section 9* "Study Procedures".

Any information, evaluations and observations, together with a narrative description of the reason(s) for which the patient discontinued the study, must be recorded in the patient source documents and in the appropriate pages in the e-CRF. The investigator should determine a primary reason for discontinuation and document it in the e-CRF.

In order to avoid missing data, patients who discontinue treatment before the first interim evaluation period (i.e., Visit 5, after 3 months of treatment) will be asked to score their rhinoconjunctivitis symptoms and rescue medication use on the e-diary during the first interim evaluation period, off study treatment.

7.4.1 Withdrawal Criteria

A patient may be withdrawn from the clinical study for any of the following reasons:

Ineligibility,

Withdrawal of consent by the patient for any reason, at any time,

Withdrawal by the Investigator for safety reasons,

Withdrawal by the Investigator for lack of compliance with the protocol,

Withdrawal by the Investigator for pregnancy during the study,

Lost to follow-up. The Investigator should document all efforts made to contact the patient. In case of failure to collect any information on the patient, he/she will be considered as lost to follow-up,

Any other reason (to be specified).

If the reason for withdrawal is an adverse event (AE), the investigator will follow the patient through resolution of the AE or until the end of the study and provide STALLERGENES with a final report of the AE or a report explaining why no final report will be available.

7.4.2 Patient Replacement Policy

Randomized patients who withdraw during this study will not be replaced.

8. TREATMENT OF PATIENT (INVESTIGATIONAL PRODUCTS AND CONCOMITANT MEDICATIONS)

8.1 Study Investigational Products

8.1.1 Description of Investigational Products

To enable the double-blind design, STG320 tablets of HDM allergen extracts (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae)* at the doses of 100 IR and 300 IR, and matching placebo tablets, Placebo 100 (P_{100}) and Placebo 300 (P_{300}), will be administered in this study.

- **Run-in phase**

Each patient eligible for the run-in period of the screening phase will be administered one tablet of Placebo 300 (P_{300}) sublingually per day, for a period of 5 weeks.

- **Study treatment phase**

Each randomized patient will receive either STG320 sublingual tablets or matching placebo.

The different total daily doses for active treatment will be obtained as follows:

Daily doses		**Active tablets**
Initiation period	100 IR on Day 1	1 tablet of 100 IR of STG320 from the initiation blisters
	200 IR on Day 2	2 tablets of 100 IR of STG320 from the initiation blisters, taken simultaneously
Maintenance period: 300 IR from Day 3 until the end of treatment		1 tablet of 300 IR of STG320 from the maintenance blisters

The different total daily placebo intakes will be obtained as follows:

Daily doses		**Placebo tablets**
Initiation period	Placebo on Day 1	1 tablet of P_{100} from the initiation blisters
	Placebo on Day 2	2 tablets of P_{100} from the initiation blisters, taken simultaneously
Maintenance period: Placebo from Day 3 until the end of treatment		1 tablet of P_{300} from the maintenance blisters

8.1.2 Packaging

IPs will be packaged, labeled and dispatched under the responsibility of subcontracted packaging company on behalf of STALLERGENES.

- **Run-in phase**

The run-in phase treatment unit for each patient will consist of 2 boxes of one blister pack card; each blister pack card will contain 20 tablets of P_{300}.

- **Study treatment phase**
  - The initiation phase treatment unit for each patient will consist of one box containing 3 blister pack cards; each blister pack card will contain one tablet of STG320 HDM allergen extracts at the dose of 100 IR or matching placebo (P_{100}).
  - The maintenance phase treatment units for each patient will consist of four boxes containing 5 blister pack cards each. Each blister pack card will contain 20 tablets of STG320 HDM allergen extracts at the dose of 300 IR or matching placebo (P_{300}).

8.1.3 Labeling

The IP will be labeled in compliance with the applicable US regulations, Canadian regulations, European Directive 2003/94/EC, Good Manufacturing Practice guidelines (Volume 4 Annex 13) and local regulations. Details of labeling and dispensing procedures will be in accordance with the standard operating procedures of subcontracted packaging company.

The labels will be adapted to local regulatory requirements, to the size of the investigational product package and translated as appropriate.

The IP labels consist of two parts: the first is a tear-off sticker which must be attached to the patient source document/medical record at the time of dispensation and the second remains fixed to the IP package.

8.1.4 Storage Requirements

Investigational products should be stored in a secured, limited access area. They do not require any special storage conditions.

The Investigator or the Pharmacist is responsible for the appropriate storage of IP at the investigative site.

The Investigator will instruct the patients/parents/legally acceptable representative to store the IP in a secure place out of the reach of children.

8.1.5 Investigational Product Dispensation

At Visit 2, eligible patients will be given 2 run-in period treatment kits consisting of 1 blister pack card (20 tablets of placebo each) for the 5-week run-in period (run-in period treatment kit numbers will be allocated through IVRS/IWRS).

At randomization (Visit 3), allocation of patients to treatment groups will proceed through the use of IVRS or IWRS. The site will be requested to enter the protocol number, the Investigator site number and the patient-specific screening number. The caller will be provided with treatment kit number(s). Each patient will receive one initiation phase treatment unit (i.e., one box containing 3 blister pack cards; each blister pack card will contain one tablet of STG320 HDM allergen extracts at the dose of 100 IR or matching placebo) and one maintenance phase treatment unit (i.e., one box containing 5 blister pack cards. Each blister pack card will contain 20 tablets of STG320 HDM allergen extracts at the dose of 300 IR or matching placebo).

At Visits 5-7, each patient will receive one maintenance phase treatment unit (i.e., one box containing 5 blister pack cards. Each blister pack card will contain 20 tablets of STG320 HDM allergen extracts at the dose of 300 IR or matching placebo).

The call/connection to IVRS/IWRS will be repeated prior to each dispensation of IP in order to obtain a treatment kit number.

Patients will be treated for approximately 12 months. The first dose (Visit 3) is to be taken in the presence of the Investigator and the patient observed for the next 30 minutes.

Subsequent doses are to be taken at home, daily, at approximately the same time in the morning. Tablets are to be taken in an empty mouth and the patient instructed to leave the tablets under the tongue until complete disintegration before swallowing. The patient is not to eat or drink before the tablet is completely disintegrated. On Day 2, the two tablets which comprise the treatment dose are to be taken simultaneously.

In the event IP is discontinued for more than 7 days, it is to be restarted under medical supervision at the dosage of last intake.

8.1.6 Monitoring of Patient Compliance

At each visit after drug is dispensed, the patients must return all unused investigational product as well as any empty boxes and blisters.

Drug reconciliation must be done in the patient's presence in order to obtain required explanations regarding any discrepancies in compliance with the dosing regimen.

The number of tablets returned and the date they were returned must be recorded in the e-CRF and the IP Accountability Form. Explanations of non-compliance must also be recorded in the e-CRF.

Compliance with study medication is defined as investigational product consumption by the patient greater than or equal to 80% of that prescribed. In case of persistent non compliance, the patient's withdrawal from the study should be considered.

8.1.7 Investigational Products (IP) Accountability

The Investigator or the Pharmacist will receive blinded numbered treatments.

A Drug Accountability Form will be supplied to the site and is to be kept up-to-date. On this form, the following information will be recorded: the treatment kit number allocated to the patient, the initials of the person who dispenses the IP to the patient, the dates of dispensation and return, and the number of returned tablets. The site monitor will check the supplies of the IP and will review the accountability records during monitoring visits and at the completion of the study.

In case of interruption of investigational product intake (permanent or temporary) the stop date has to be documented in the e-CRF. For temporary interruptions, the resume date must also be recorded.

Partially used treatment boxes or blister cards must never be used for another patient.

After completion of the study, all used (including empty containers) and unused IP boxes must be reconciled and returned to the subcontracted packaging company.

8.2 Concomitant Treatments and Rescue Medications

8.2.1 Concomitant Treatments

An accurate record of all medications other than the IP must be kept in the clinic chart/patient's medical record (source documentation) and in the e-CRF. This record should include the generic name of the drug, the dose, the date(s) of administration, and the indication for use.

Patients will be instructed to record all intake of concomitant medications in the "Adverse Event and Concomitant Medication Card."

The use of concomitant medication will be reviewed during the Data Review Meeting (DRM) prior to database lock and unblinding to assess protocol deviation and their potential impact on study results.

8.2.2 Rescue Medications

Patients will be supplied with antihistamines, intranasal corticosteroids, and oral corticosteroids as rescue medications. Beginning at Visit 2 and thereafter, as necessary through Visit 8, antihistamines and intranasal corticosteroids will be provided to patients for managing allergic rhinitis symptoms. No other rescue medications should be taken by the patients without authorization of the Investigator.

If AR symptoms are not sufficiently alleviated despite these treatments, the Investigator will evaluate with the patient if systemic corticosteroid is indicated and will prescribe this treatment.

Management of allergic rhinoconjunctivitis rescue medications will follow a stepwise regimen:

Step 1: Antihistamine

Patients will be instructed to initiate treatment of AR symptoms with oral antihistamine (e.g., cetirizine 10 mg, 1 tablet daily in the morning).

In cases where ocular allergic symptoms are present (i.e., itchy/red eyes and/or watery eyes) and the oral antihistamine is not sufficient to control the ocular symptoms, topical antihistamine by the ocular route can be added (e.g., olopatadine 0.1% eye drops).

Note: Use of topical nasal antihistamines and decongestants (e.g., azelastine, phenyephrine, oxymetazoline) is not permitted during the study.

Step 2: Intranasal corticosteroid

If the allergic rhinitis symptoms are not sufficiently alleviated by treatment with oral antihistamine (step 1), patients are to be instructed to initiate treatment with intranasal corticosteroid (e.g., budesonide aqueous nasal spray, 64 μg/nostril daily in the morning, total of 128 μg/day), with or without oral antihistamine.

In cases where ocular allergic symptoms are present, topical antihistamine by the ocular route may be continued. While a decrease in nasal symptoms may occur as soon as 12 hours after starting treatment, it may take several days to reach the maximum effect. Therefore, it is recommended that treatment with intranasal corticosteroid be maintained for a minimum of 4 consecutive days and intermittent use of intranasal corticosteroid should be discouraged.

Step 3: Oral corticosteroid

If the allergic rhinitis symptoms are not sufficiently alleviated by intranasal corticosteroid (step 2), the patient should consult the Investigator and treatment with oral corticosteroid should be considered: prednisolone at a dose adapted to the patients' weight and to their symptom severity. Previously used intranasal corticosteroid with or without oral antihistamine will be

continued concomitantly with the step 3 treatment. The treatment with oral corticosteroid should be gradually reduced and stopped after 5 to 10 days and treatment with step 2 therapy (intranasal corticosteroid) continued.

In cases where ocular allergic symptoms are present, topical antihistamine by the ocular route may be continued.

The patient's supply of rescue medication will be checked at each visit and replenished, as needed.

Apart from the management of AEs, no anti-allergy medication other than the rescue medication is to be taken by a patient unless it has been agreed with the investigator and with STALLERGENES, as this will constitute a protocol deviation. Any antihistamine or corticosteroid treatments, even those provided as rescue medication, taken for a reason other than as treatment for allergic rhinitis symptoms due to HDM, is to be reported in the e-CRF as concomitant medication.

8.2.3 Epinephrine Auto-Injector

8.2.3.1 Special Warnings and Precautions

Treatment with allergen immunotherapy can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal edema that require treatment with epinephrine.

Study participation may not be suitable for patients with certain medical conditions that may reduce the ability to survive a serious allergic reaction or increase the risk of adverse reactions after epinephrine administration. Examples of these medical conditions include but are not limited to: markedly compromised lung function (either chronic or acute), unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension. In addition, study participation may not be suitable for patients who are taking medications that can potentiate or inhibit the effect of epinephrine. These medications include beta-adrenergic blockers, alpha-adrenergic blockers, ergot alkaloids, tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, cardiac glycosides, and diuretics.

Adequate resuscitation equipment and facilities for managing severe allergic reactions must be available at each study site.

Patients will be provided with a study site-specific contact phone number and be instructed to call at any time for questions about any adverse reactions they may experience.

8.2.3.2 Safety and Emergency Procedures

At Visit 3, patients will be instructed to recognize the signs and symptoms of a severe allergic reaction. They will be trained on the proper use of emergency self-injection of epinephrine. Patients will receive an epinephrine auto-injector to be used in case of a severe allergic reaction. Patients will be instructed to seek immediate medical care upon its use. They are to discontinue study therapy and contact the study site as soon as possible for further evaluation. The epinephrine auto-injector will be replaced as necessary.

8.2.4 Prohibited Concomitant Treatments (Medications and Therapies)

8.2.4.1 Prohibited Treatments During the Screening Phase

Before SPT and spirometry are performed certain medications must be stopped and wash-out periods observed. Patients entering the run-in period (Visit 2) will be provided with oral antihistamine and intranasal corticosteroid as rescue medication to treat symptoms of allergic rhinitis. If a patient was using different treatments than the study rescue medications before entering the run-in period, s/he will have to switch to the rescue medications provided for the study and respect the wash-out periods described below. During the run-in period, the stepwise regimen for use of rescue medication will apply (*Section 8.2.2* "Rescue Medications").

The prohibited medications and the corresponding wash-out periods are described below:

Prohibited medication before SPT and before entering the Run-in period	**Wash-out period At least:**
Short-acting antihistamines (e.g., acrivastine, diphenhydramine, chlorpheniramine, doxepine)	3 days before SPT or start of run-in period
Long-acting antihistamines (e.g., cetirizine, fexofenadine, loratadine, desloratadine, azelastine, ebastine),	7 days before SPT or start of run-in period
Astemizole	10 days before SPT or start of run-in period
Hydroxyzine, ketotifen, tricyclic antidepressants and Monoamine oxidase inhibitors	14 days before SPT or start of run-in period
Moderate-high dose topical steroids on the forearm	14 days before SPT
Oral or systemic corticosteroids	30 days before SPT or start of run-in period
Long Acting Systemic corticosteroids	90 days before or start of run-in period
Anti-IgE (Omalizumab)	60 days before SPT or start of run-in period
Immunosuppressive drugs	90 days before SPT or start of run-in period
Prohibited medication for Spirometry	**Wash-out period At least:**
Short-acting beta 2-agonists (SABA) or anticholinergic agent (ipratropium bromide)	6 hours prior to spirometry testing

8.2.4.2 Prohibited Concomitant AR Treatments During Run-in and Treatment Phase

Except for the rescue medications provided as part of the study or for asthma controller treatments initiated before patient selection, continuation or initiation of any other anti-allergic medications are not permitted after randomization.

The following are prohibited:

From Visit 2 (baseline) to Visit 9 (End of Treatment Phase):

- Oral antihistamines, including ketotifen (except those provided as rescue medications) and intranasal antihistamine
- Oral, systemic and intranasal corticosteroids (except those provided as rescue medications)
- Cromone: cromoglycate and nedocromil
- Anti-leukotrienes (if not used before patient selection as asthma controller treatment)
- Theophylline or inhaled corticosteroid (if not used before patient selection as asthma controller treatment) and Long acting Beta 2 agonist (refer to asthma patients exclusion criteria)
- Long-acting anticholinergic agents (e.g., tiotropium bromide)
- Anti-IgE
- Decongestants (oral, nasal, or ophthalmic)
- Any topical nasal or ocular treatments except those provided as rescue medications
- Beta-blocker therapy whatever the route
- Tricyclic antidepressants and mono amine oxidase inhibitors (MAOIs)

If one of these treatments becomes required during the course of the study, the investigator is to liaise with the Sponsor to determine if the patient may remain in the study.

8.2.5 Maintenance Asthma Therapy (When Used)

Asthmatic patients eligible to participate in the study will be those with asthma controlled by treatment(s) consistent with GINA 2014 treatment Steps 1 or 2 (*Appendix II*).

The following asthma treatments are permitted during the study: reliever treatment with as needed short acting β2-agonist with or without controller treatment consisting of low dose inhaled corticosteroid (i.e., ≤400 µg of budesonide/day or equivalent dose of other corticosteroid) or leukotriene receptor antagonist or low dose theophylline.

If a patient requires adaptation of their asthma treatment, s/he should return to the investigator for medical assessment.

9. STUDY PROCEDURES

9.1 Patient Identifier

All patients who have signed an Informed Consent Form (ICF) or Assent Form together with their parent(s)/legal representative in the case of adolescents, whether they are randomized in this study or not, will receive a screening number allocated in ascending order of screening.

9.2 Description of Procedures

9.2.1 Informed Consent Form

At Visit 1, an Informed Consent Form (ICF) has to be dated and signed by the patient (and parent(s)/legal representative in the case of adolescents) before any study procedure may be performed.

If the patient is <16 years old, an assent form will be used instead of the informed consent form in addition to the ICF dated and signed by the parents. If the patient is aged between 16 and <18 years old, s/he may sign an ICF on her/his own, or sign an assent form in addition to the ICF signed by the parent(s)/legal representative, depending on the local regulations.

The Investigator who informs the patient (and parent(s)/legal representative) and obtains their written consent/assent has to also date and sign the ICF/Assent form. A copy of the ICF /Assent form will be given to the patient (and parent(s)/legal representative) and the original is to be retained by the Investigator.

9.2.2 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria should be checked at Visit 1 and Visit 2 (run-in) and confirmed before randomization at Visit 3. To be randomized in the study, a patient must meet all the inclusion criteria and none of the exclusion criteria.

At the Investigator's discretion a Nasal Provocation Test for HDM may be performed to confirm the diagnosis of HDM-associated AR. The study site's standard practice should be followed.

9.2.3 Medical and Allergy History

Medical history including complete allergy history will be collected at Visit 1.

9.2.4 Demographic Data, Height and Weight

Information on gender, date of birth, ethnic origin, height and weight will be collected at Visit 1.

9.2.5 Prior and Concomitant Medication

At Visit 1, AR and asthma medications taken within the six previous months will be recorded. During the study, any intake of medication will be reported by the Investigator in the medical source data and in the e-CRF. Information regarding drug name (generic name), total daily dose, route, start and end date or whether ongoing, and indication for use will be recorded.

9.2.6 Physical Examination and Vital Signs

At Visits 1 and 9, a physical examination will be conducted including vital signs (systolic and diastolic blood pressure, and pulse rate), and examination of the skin, eyes, ears, nose, throat, cardiovascular, respiratory, gastrointestinal, musculoskeletal and nervous systems.

At Visits 2 through 8, and at Visit 10, a directed physical examination will be performed if judged necessary by the investigator based on symptoms and physical signs.

9.2.7 Skin Prick Test

At Visit 1, Skin Prick Testing [*Heinzerling et al.,2005; Heinzerling et al.,2009*] will be performed using the following battery of aeroallergens: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, cockroach, *Aspergillus, Cladosporium*, *Parietaria,* and *Alternaria* and other geographically relevant, potentially confounding aeroallergens such as cypress, birch, grass, ragweed… as well as positive (histamine dihydrochloride) and negative (saline diluent) controls.

SPT allergens used in this study will be provided by the Sponsor using locally approved extracts. Testing is to be performed according to the USPI/Summary of Product Characteristics.

For the HDM allergens, *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae,* a test will be considered positive when, 20 minutes after testing, the largest wheal diameter is at least 5 mm greater than that of the negative control. For the other allergens, a wheal diameter at least 5 mm greater than the negative control will be considered positive.

The tests will be considered valid when the positive control induces a wheal diameter of at least 3 mm and negative control induces a wheal diameter less than 2 mm. In the event of non valid controls or borderline results, the SPT should be repeated.

The outline of wheals (and, if present, pseudopods and satellites) will be traced with a sharp black felt pen. The real limits of the wheal are confirmed by palpation. Hypoallergenic transparent adhesive tape will be applied on the tracings and will be then transferred on the source document sheet.

Wash-out periods for specific categories of medications are provided in *Section 8.2.4.1* "Prohibited Treatments During the Screening Phase."

9.2.8 Spirometry

At Visit 1, lung function testing will be performed according to American Thoracic Society/European Respiratory Society (ATS/ERS) Task Force: Standardization of Lung Function Testing [*Miller et al.,2005*] (see *Appendix I*). The Forced Vital Capacity/Forced Expiratory Volume in one second (FEV_1) maneuver will be performed three times and the best of the values will be retained. To be eligible for enrollment, the FEV_1 must be at least 80% of the predicted value. Ethnic corrective factors may be used in accordance with the recommendations of the equipment manufacturer.

At Visit 3 and Visit 9, lung function testing will be repeated only for asthmatic patients.

9.2.9 Classification of Asthma Status

At Visit 1, the asthma status (Yes or No) of all patients will be assessed.

If present, asthma will be classified according to the GINA Guidelines (Global Initiative for Asthma – GINA 2014 – ref. *Appendix II* and *Appendix III*).

Eligible asthmatic patients will be those with asthma, controlled by treatment(s) consistent with GINA 2014 treatment Steps 1 or 2 [i.e., reliever treatment with as needed short acting β2-agonist with or without controller treatment consisting of low dose inhaled corticosteroid (≤400 µg of budesonide/day or equivalent dose of other corticosteroid) or leukotriene receptor antagonist or low dose theophylline].

9.2.10 Blood sampling

At Visits 1 and 9, blood samples (approximately 20 mL) will be drawn at for:

- Safety laboratory tests:

  Hematology (i.e., hemoglobin, hematocrit, red blood cells (RBC), platelets, white blood cells (WBC), differential count (neutrophils, basophils, eosinophils, monocytes, lymphocytes)

  Biochemistry (i.e., sodium, potassium, chloride, creatinine, glucose, bilirubin (direct, indirect, total), ASAT (SGOT), ALAT (SGPT), Gamma Glutamyl Transferase (GGT)

- Immunological markers (IgE and IgG_4 specific for *D. pte* and *D. far* allergens)

Blood safety laboratory tests and measurement of immunological markers will be performed by a subcontracted Central Laboratory. Study sites will be provided with a separate laboratory manual and with laboratory kit material. The laboratory manual contains the sampling, handling and shipment procedures.

[redacted]

9.2.12 Pregnancy Test

At Visits 1 and 3, a urinary pregnancy test will be performed on all females of childbearing potential.

Females are considered not to have childbearing potential prior to menarche, at least 2 years after menopause, or if they have had a total hysterectomy, bilateral oophorectomy or ovariectomy.

Urine pregnancy tests will be provided by STALLERGENES.

9.2.13 IVRS/IWRS

Allocation of patients to treatment groups will proceed through the use of an Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS). The site will be requested by the IVRS/IWRS to enter the protocol number, the Investigator site number and the screening number. The caller will be provided with treatment kit number(s).

The call/connection to IVRS/IWRS will be repeated prior to each dispensation of IP.

9.2.14 Dispensation and Use of the Electronic Diary (e-diary)

At Visit 2, each patient will be provided with an electronic diary (e-diary) and will be instructed by site staff as to how and when to score their allergic rhinoconjunctivitis symptoms (i.e., itchy nose, sneezing, runny nose, blocked nose, itchy/red eyes and watery eyes) and record their use of rescue medication. Site staff should emphasize to the patient the importance of the accurate and regular completion of the e-diary. Patients will be asked to bring the device to each visit.

Symptom scoring and recording of rescue medication use are to be performed daily during the 5-week run-in period, the two weeks prior to Visits 5, 6, and 7 (interim evaluation periods at Months 3, 6, and 9) and during the 4 weeks between Visits 8 and 9 (primary evaluation period, Month 12).

The assessment will address symptom intensity over the previous 24 hours and is to be performed at the same time every morning after awakening, using the following 4-point scale:

0 = no symptom

1 = mild symptom; symptom clearly present, but minimal awareness; easily tolerated

2 = moderate symptom; definite awareness of symptom that is bothersome but tolerable

3 = severe symptom; symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping

- Patients will be supplied with antihistamines, intranasal corticosteroids, and oral corticosteroids as rescue medications. Beginning at Visit 2 and thereafter, as necessary through Visit 8, antihistamines and intranasal corticosteroids will be provided to patients for managing allergic rhinitis symptoms. If AR symptoms are not sufficiently alleviated despite these treatments, the Investigator will evaluate with the patient if systemic corticosteroid is indicated and will prescribe this treatment. For a description of the stepwise treatment regimen *Section 8.2.2* "Rescue Medications." Patients are to record their rescue medication use over the previous 24 hours.
- A Visual Analogue Scale (VAS), comprising 101 pixels (0-100), ranging from "absence of symptoms" (score = 0) to "very severe symptoms" (score = 100), will be completed by the patient weekly basis (at the end of each week) during the run-in period, the interim evaluation periods and the primary evaluation period.
- The data from the e-diary device will be automatically transmitted to the study database. Patient compliance with data recording is to be monitored by the site staff via a dedicated web portal. In addition, an alert will be sent to the study center in case of patient's non completion or non transmitted data.
- At Visit 9, the site staff will collect the e-diary device and deactivate it.

9.2.15 Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)≥12)

The RQLQ was developed to evaluate the impact of rhinoconjunctivitis symptoms on quality of life [*Juniper et al.,1999*]. It is designed to evaluate the change in a patient's quality of life over some period of time. The RQLQ(S)≥12 was developed subsequently to enable the evaluation of adolescents 12-17 years of age in addition to adults. It consists of 28 questions, divided into seven domains as follows: Activities (3 questions), Sleep (3 questions), Non-nose/eye symptoms (7 questions), Practical problems (3 questions), Nasal symptoms (4 questions), Eye symptoms (4 questions) and Emotional (4 questions). Patients are asked to recall their experiences during the previous week and to give their responses on a 7-point Likert scale (lower being better).

In this study, the self-administered questionnaire is to be completed by the patient at the study site at Visit 3 (before first dosing) and Visit 9.

9.2.16 Global Rating of Change Questionnaire

The global evaluation of the efficacy of study therapy relative to the allergic symptoms during the baseline evaluation period is to be assessed by the patient at Visit 9.

The following 15-point Likert scale will be used [*Juniper et al.,1994*]:

Symptom improvement:

1 = Almost the same, hardly any better at all

2 = a little better

3 = somewhat better

4 = moderately better

5 = a good deal better

6 = a great deal better

7 = a very great deal better

0 = No change

Symptom worsening

1 = Almost the same, hardly any worse at all

2 = a little worse

3 = somewhat worse

4 = moderately worse

5 = a good deal worse

6 = a great deal worse

7 = a very great deal worse

9.2.17 Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI + CIQ: AS)

The Work Productivity and Activity Impairment (WPAI) Questionnaire plus Classroom Impairment Questions (CIQ), Allergy Specific (AS) is a patient-reported quantitative assessment of the amount of absenteeism (work time missed), presenteeism (impairment at work / reduced on-the-job effectiveness), work productivity loss (overall work impairment / absenteeism plus presenteeism) and regular daily activity impairment attributable to allergy (moderate-to-severe allergy symptoms).

It is a 9-item self-administered questionnaire assessing the patient's productivity and allergy-induced activity impairment during the past seven days.

This questionnaire will be completed by the patient at the study site at Visit 3 (before first dosing) and at Visit 9.

9.2.18 EQ-5D-5L Generic Health-Related Quality of Life

The EQ-5D describes the patients' health state using 5 dimensions, namely: 1. Mobility, 2. Self-care, 3. Usual activities, 4. Pain/Discomfort and 5. Anxiety/Depression. Each dimension is evaluated on a 5-point scale: no problems / slight problems / moderate problems / severe problems / extreme problems. The responses are then transformed into a single index by applying a formula that attaches weights to each of the response levels in each dimension. The patients also assess their overall health on a VAS ranging from 0 ("the worst health you can imagine") to 100 ("the best

health you can imagine") [*Herdman et al.,2011*]. This questionnaire will be completed by the patient at the study site at Visit 3 (before first dosing) and Visit 9.

9.2.19 HDM Avoidance Measures Questionnaire

At Visit 9, patients will be asked to indicate any and all HDM avoidance measures/interventions implemented at their home since they entered the study (e.g., encasing mattresses, pillows and/or quilts in mite impermeable covers, replacement of mattress, pillows and/or quilts, regular washing of bedding in hot temperature (55-60°C) water, replacement of carpets, removing carpeting in favor of hard flooring, use of acaricides and/or tannic acid).

9.2.20 Adverse Events/Concomitant Medication Card

Patients will be given an Adverse Events/Concomitant Medication card (AE/Conc. Med. card) to report any changes in their medical condition and use of any concomitant medication throughout the study.

The AE/Conc. Med. card will be issued at Visit 1 and will have to be brought back to the study site at Visit 2, collected by the Investigator and discussed with the patient. A new AE/Conc. Med. card will be issued at each subsequent visit, and discussed and collected the visit thereafter.

Any adverse reactions/events and/or concomitant medication use should be reported in the patient's medical chart and, in the e-CRF.

9.3 Visit by Visit Description

9.3.1 Visit 1 (Selection Visit)

- Before any study procedures are performed, the Investigator/co-Investigator must obtain the signed informed consent form from the patient/legal guardian, as applicable, according to local laws and requirements. Signed assent should be obtained from adolescents in addition to the informed consent form signed by the parent/legal guardian.
- The site staff will access IVRS/IWRS to obtain a screening number.
- The Investigator/co-Investigator will check the patient's eligibility (inclusion/exclusion criteria).
- The Investigator/co-Investigator will record the patient's medical history and prior and concomitant medication use over the previous 6 months.
- Patient date of birth, ethnic origin, gender, height and weight will be collected.
- Vital signs will be measured (after 5 min rest) and a physical examination will be performed.
- Spirometry will be performed.
- Asthma status (Yes/No) will be assessed. If present, asthma will be further categorized according to GINA 2014 treatment Step and level of control.

- Skin Prick Test (SPT) will be performed after verification that no medication that could interfere with the results has been taken during the prohibited period (*Section 8.2.4* "Prohibited Concomitant Treatments (Medications and Therapies)". The following allergens should be tested: *D pteronyssinus*, *D. farinae* and a battery including cat, dog, cockroach, Aspergillus, Cladosporium, Parietaria and Alternaria, and other geographically relevant potentially confounding allergens such as cypress, birch, grass, ragweed… as well as positive (histamine dihydrochloride) and negative (saline diluent) controls.

Note: At the Investigator's discretion a Nasal Provocation Test for HDM may be performed to confirm the diagnosis of HDM-associated AR. The study site's standard practice should be followed.

- In patients with positive SPT to *D. pte* and/or *D. far*, a blood draw will be performed for:
  - Laboratory tests (hematology and biochemistry).
  - Immunological markers.

- A urine pregnancy test will be performed for all female patients of childbearing potential.
- Patient will be provided with a paper-card allowing him/her to record any adverse event(s) occurred and medication(s) taken (other than those of the study protocol) between this visit and the next visit. The patient is to be instructed to bring this card back to the site at the next visit.
- The Investigator will instruct the patient not to change his/her daily environment in relation to HDM exposure during the conduct of the study.
- An appointment will be made for Visit 2 for all eligible patients.

9.3.2 Visit 2 (Run-in period Visit)

- Patients meeting all the selection criteria will enter a single-blind placebo run-in period of 5 weeks (including the baseline evaluation period). This 5-week period is to be selected based on the patient's history of HDM-related rhinitis symptoms and the investigator's knowledge of the peak season for HDM in the area. The Investigator/co-Investigator must check the patient eligibility (inclusion/exclusion criteria), in particular the HDM-specific IgE levels.
- The Investigator/co-Investigator should check the "AE/Concomitant Medication" paper card provided to the patient at the previous visit. Adverse events and concomitant medication will be recorded. A physical examination will be performed depending on medical findings, if any.
- A new "AE/Concomitant Medication" paper card will be provided to the patient, to be brought back at the next visit.
- The Investigator/co-Investigator is to call the IVRS or connect to IWRS in order to obtain the run-in phase treatment kit numbers.

- The Investigator/co-Investigator will dispense the placebo sublingual tablets and instruct the patient to take one tablet sublingually every day at approximately the same time (in an empty mouth) for a period of 5 weeks. The patient must be instructed to leave the tablets under the tongue until complete disintegration before swallowing. Patient is not to eat or drink before the tablet is completely disintegrated. The first dose should be taken under the supervision of the Investigator/co-Investigator and the patient monitored for 30 minutes. The patient should be instructed to return blisters and box (whether empty/used or unused) to the study site at the next visit.
- The Investigator/co-Investigator will dispense the rescue medication (RM) and instruct the patient that RM is to be used to treat at least moderate allergic rhinitis symptoms (i.e., one or more symptoms that are at a minimum bothersome but tolerable). Patients will be instructed regarding the stepwise regimen to be followed (*Section 8.2.2* "Rescue Medications").
- The e-diary will be activated by the study site staff and this device will be provided to the patient. A detailed training will be provided to the patient to ensure the full understanding of how the device is to be used. The patient will be instructed to score his/her rhinoconjunctivitis symptoms and rescue medication use daily, in the morning, and the VAS weekly, for a period of 5 weeks (*Section 9.2.14* "Dispensation and Use of the Electronic Diary (e-diary)").
- An appointment for Visit 3 will be made for all eligible patients.

9.3.3 Visit 3 (Randomization Visit)

- This visit is to be performed within the 7 days following the 5-week run-in period.
- The Investigator/co-Investigator must confirm the patient eligibility (inclusion/exclusion criteria), in particular that the Baseline Average TCS was ≥5/15 during the last 4 weeks of the run-in period. Spirometry will be repeated only for asthmatic patients.
- The Investigator/co-Investigator should check the "AE/Concomitant Medication" paper card provided to the patient at the previous visit. Adverse events and concomitant medication will be recorded. A physical examination will be performed depending on medical findings, if any.
- A new "AE/Concomitant Medication" paper card will be provided to the patient, to be brought back at the next visit.
- The site staff checks that the box and blisters of the placebo tablets are returned by the patient. The "Drug Accountability Form" should be kept up-to-date by the study site staff.
- The Investigator/co-Investigator should check the completion of the e-diary via the web portal.
- Urine pregnancy test for all female patients of childbearing potential will be performed.
- Patient self-administered questionnaires should be completed at the site prior to the first investigational product (IP) administration: Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)≥12), Work Productivity and Activity Impairment (WPAI) Questionnaire plus Classroom Impairment Questions (CIQ), Allergy Specific (AS), EQ-5D.

- The Investigator/co-Investigator is to call the IVRS or connect to IWRS in order to obtain two treatment kit numbers (one for escalation phase and one for maintenance phase): patients will be randomized and assigned to one of the two treatment groups.
- The IP will be dispensed to the patient and the IP kit numbers will be entered in the e-CRF. The tear-off labels will be affixed to the patient's medical records. Patient will be instructed to bring back the IP boxes and blisters (whether empty/used or unused) to the site at the next visit.
- The first dose of IP is to be taken at the site under the supervision of the Investigator and the patient monitored for at least 30 minutes. The patient must be instructed to keep the tablet under the tongue until complete disintegration before swallowing. The patient is not to eat or drink before the tablet is completely disintegrated.
- All used and unused rescue medication (RM) previously dispensed should be checked and the "Drug Accountability Form" should be kept up-to-date. Resupply of RM may be provided, as necessary.
- Patient will be provided with an epinephrine auto-injector and instructed and trained in its use (*Section 8.2.3* "Epinephrine Auto-Injector").
- [redacted]
- An appointment will be made for Visit 4, 1 month after Visit 3.
- In order to prevent missing data, patients who discontinued the treatment before the first interim evaluation period (i.e., before 3 months of treatment) will be asked to continue the study (without study treatment) until Visit 5 (i.e., until the end of the first interim evaluation period). Patients will be asked to score their rhinoconjunctivitis symptoms and rescue medication use on the e-diary during the first interim evaluation period.

9.3.4 Visit 4 (Month 1 Visit)

- This visit is to be performed 30 days +/- 4 days after Visit 3.
- The Investigator/co-Investigator should check the "AE/Concomitant Medication" paper card provided to the patient at the previous visit. Adverse events and concomitant medication will be recorded. A physical examination will be performed depending on medical findings, if any.
- A new "AE/Concomitant Medication" paper card will be provided to the patient, to be brought back at the next visit.
- IP boxes and blisters dispensed at the previous visit should be checked and given back to the patient. The "Drug Accountability Form" should be kept up-to-date by the study site staff. Patient will be reminded to bring back the IP boxes and blisters (whether empty/used or unused) to the site at the next visit.

- All used and unused rescue medication (RM) previously dispensed should be checked and the "Drug Accountability Form" should be kept up-to-date. Resupply of RM may be undertaken, as necessary.
- Patient will be instructed that the scoring of rhinoconjunctivitis symptoms and recording of RM consumption and completion of the VAS is to be started 2 weeks before the next visit (Visit 5). Patients will be informed that during this 2-week evaluation period, VAS should be completed on a weekly basis, and scoring of rhinoconjunctivitis symptoms and RM consumption should be recorded on a daily basis (*Section 9.2.14* "Dispensation and Use of the Electronic Diary (e-diary)").
- An appointment will be made for Visit 5.

9.3.5 Visit 5 (Month 3 Visit)

- This visit is to be performed 90 days +/- 7 days after Visit 3. In preparation for Visit 5, the site staff should check (approximately 1 week after the start of the recording period) the web portal to confirm that the patient started to properly complete the e-diary. If it is not the case, the staff should call the patient and remind him/her of the necessity to record their data in the e-diary. The Investigator/co-Investigator will monitor the quality of the data recorded by the patient in the e-diary, and correct or retrain the patient as needed.
- The Investigator/co-Investigator should check the "AE/Concomitant Medication" paper card provided to the patient at the previous visit. Adverse events and concomitant medication will be recorded. A physical examination will be performed depending on medical findings, if any.
- A new "AE/Concomitant Medication" paper card will be provided to the patient, to be brought back at the next visit.
- IP boxes and blisters dispensed at the previous visit should be checked and collected. The "Drug Accountability Form" should be kept up-to-date by the study site staff.
- The Investigator/co-Investigator is to call the IVRS or connect to IWRS in order to obtain one treatment kit number (maintenance phase).
- The IP will be dispensed to the patient and the IP kit number will be entered in the e-CRF. The tear-off label will be affixed in the patient's medical records. Patient will be reminded to bring back the IP box and blisters (whether empty/used or unused) to the site at the next visit.
- All used and unused rescue medication (RM) previously dispensed should be checked and the "Drug Accountability Form" should be kept up-to-date. Resupply of RM may be undertaken, as necessary.
- Patient will be instructed that the scoring of rhinoconjunctivitis symptoms and recording of RM consumption and completion of the VAS is to be started 2 weeks before the next visit (Visit 6). Patients will be informed that during this 2-week evaluation period, VAS should be completed on a weekly basis, and scoring of rhinoconjunctivitis symptoms and RM

consumption should be recorded on a daily basis (*Section 9.2.14* "Dispensation and Use of the Electronic Diary (e-diary)").

- An appointment will be made for Visit 6.

9.3.6 Visit 6 (Month 6 Visit)

- This visit is to be performed 180 days +/- 7 days after Visit 3.
- In preparation for Visit 6, the site staff should check the web portal (approximately 1 week after the start of the recording period) to confirm that the patient started to properly complete the e-diary. If it is not the case, the staff should call the patient and remind him/her of the necessity to record their data in the e-diary. The Investigator/co-Investigator should check the "AE/Concomitant Medication" paper card provided to the patient at the previous visit. Adverse events and concomitant medication will be recorded. A physical examination will be performed depending on medical findings, if any.
- A new "AE/Concomitant Medication" paper card will be provided to the patient, to be brought back at the next visit.
- IP box and blisters dispensed at the previous visit should be checked and collected. The "Drug Accountability Form" should be kept up-to-date by the study site staff.
- The Investigator/co-Investigator is to call the IVRS or connect to IWRS in order to obtain one treatment kit number (maintenance phase).
- The IP will be dispensed to the patient and the IP kit number will be entered in the e-CRF. The tear-off label will be affixed to the patient's medical records. Patient will be reminded to bring back the IP box and blisters (whether empty/used or unused) to the site at the next visit.
- All used and unused rescue medication (RM) previously dispensed should be checked and the "Drug Accountability Form" should be kept up-to-date. Resupply of RM may be undertaken, as necessary.
- The Investigator/co-Investigator will monitor the quality of the data recorded by the patient in the e-diary, and correct or retrain the patient as needed.
- Patient will be instructed that the scoring of rhinoconjunctivitis symptoms and recording of RM consumption and completion of the VAS is to be started 2 weeks before the next visit (Visit 7). Patients will be informed that during this 2-week evaluation period, VAS should be completed on a weekly basis, and scoring of rhinoconjunctivitis symptoms and RM consumption should be recorded on a daily basis (*Section 9.2.14* "Dispensation and Use of the Electronic Diary (e-diary)").
- An appointment will be made for Visit 7.

9.3.7 Visit 7 (Month 9 Visit)

- This visit is to be performed 270 days +/- 7 days after Visit 3.

- In preparation for Visit 7, the site staff should check the web portal (approximately 1 week after the start of the recording period) to confirm that the patient started to properly complete the e-diary. If it is not the case, the staff should call the patient and remind him/her of the necessity to record their data in the e-diary. The Investigator/co-Investigator will monitor the quality of the data recorded by the patient in the e-diary, and correct or retrain the patient as needed.
- The Investigator/co-Investigator should check the "AE/Concomitant Medication" paper card provided to the patient at the previous visit. Adverse events and concomitant medication will be recorded. A physical examination will be performed depending on medical findings, if any.
- A new "AE/Concomitant Medication" paper card will be provided to the patient, to be brought back at the next visit.
- IP box and blisters dispensed at the previous visit should be checked and collected. The "Drug Accountability Form" should be kept up-to-date by the study site staff.
- The Investigator/co-Investigator is to call the IVRS or connect to IWRS in order to obtain one treatment kit number (maintenance phase).
- The IP will be dispensed to the patient and the IP kit number will be entered in the e-CRF. The tear-off label will be affixed to the patient's medical records. Patient will be reminded to bring back the IP box and blisters (whether empty/used or unused) to the site at the next visit.
- All used and unused rescue medication (RM) previously dispensed should be checked and the "Drug Accountability Form" should be kept up-to-date. Resupply of RM may be undertaken, as necessary.
- Patient will be instructed that the scoring of rhinoconjunctivitis symptoms and recording of RM consumption and completion of the VAS is to be started 4 weeks after the next visit (Visit 8). Patients will be informed that during this 4-week evaluation period, VAS should be completed on a weekly basis, and scoring of rhinoconjunctivitis symptoms and RM consumption should be recorded on a daily basis (*Section 9.2.14* "Dispensation and Use of the Electronic Diary (e-diary)").
- An appointment will be made for Visit 8.

9.3.8 Visit 8 (Month 11 Visit)

- This visit is to be performed 323 to 330 days after Visit 3. For patients who enter the study in late winter or spring (from February to June), Visit 8 should be anticipated to avoid as much as possible unfavorable conditions for mite exposure and prevent confounding symptoms to seasonal allergens; however, it should not be performed earlier than 270 days after Visit 3.
- During Visit 8, the Investigator/co-Investigator will instruct the patient to score his/her allergic symptoms and record RM use daily and complete the VAS weekly for the next 4 weeks (i.e., until Visit 9). This 4-week period will represent the primary evaluation period and should be performed close to the 4 weeks as the baseline evaluation period. The good functioning of the e-diary will be verified. Verification of e-diary recording by the patient will be checked

approximately 1 week after the start of the period. If needed, the patient may be contacted by the study team to discuss the detected issues.

- The Investigator/co-Investigator should check the "AE/Concomitant Medication" paper card provided to the patient at the previous visit. Adverse events and concomitant medication will be recorded. A physical examination will be performed depending on medical findings, if any.
- A new "AE/Concomitant Medication" paper card will be provided to the patient, to be brought back at the next visit.
- IP box and blisters dispensed at the previous visit should be checked and given back to the patient. The "Drug Accountability Form" should be kept up-to-date by the study site staff. Patient will be instructed to bring the IP box and blisters (whether empty/used or unused) back to the site at the next visit.
- All used and unused rescue medication (RM) previously dispensed should be checked and the "Drug Accountability Form" should be kept up-to-date. Resupply of RM may be undertaken, as necessary.
- An appointment will be made for Visit 9.
- Approximately one week after Visit 8, the site staff should check the web portal to confirm that the patient started to properly complete the e-diary. If it is not the case, the staff should call the patient and remind him/her of the necessity to record their data in the e-diary. The Investigator/co-Investigator will monitor the quality of the data recorded by the patient in the e-diary, and correct or retrain the patient as needed.

9.3.9 Visit 9 (Month 12, End of Treatment Visit)

- This visit is to be performed 360 to 367 days after Visit 3. For patients who enter the study in late winter or spring (from February to June), Visit 9 should be anticipated to avoid as much as possible unfavorable conditions for mite exposure and prevent confounding symptoms to seasonal allergens; however, it should not be performed earlier than 300 days after Visit 3.
- The Investigator/co-Investigator will monitor the quality of the data recorded by the patient in the e-diary, and will deactivate the device.
- Patient will be asked to complete the questionnaire relative to the HDM avoidance measures implemented (if any) at their residence since Visit 1. The Investigator should question the patient and record any change in the patient's environment in relation to HDM exposure during the study in the e-CRF.
- A complete physical examination will be performed and vital signs measured (after 5 min rest) (*Section 9.2.6* "Physical Examination and Vital Signs").
- Spirometry will be performed in asthmatic patients only.
- Blood collection will be done for:
  - Laboratory tests (hematology and biochemistry)

– Immunological markers

[redacted]

- The Investigator/co-Investigator should check the "AE/Concomitant Medication" paper card provided to the patient at the previous visit. Adverse events and concomitant medication will be recorded.
- Patient self-administered questionnaires are to be completed at the site: Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)≥12), Work Productivity and Activity Impairment (WPAI) Questionnaire plus Classroom Impairment Questions (CIQ), Allergy Specific (AS), and EQ-5D-5L.
- Patient should complete the Global Rating of Change Questionnaire at the site.
- IP boxes and blisters (whether empty/used or unused) should be collected and checked, and the "Drug Accountability Form" kept up-to-date by the study site staff.
- All used and unused RM previously dispensed should be collected and the "Drug Accountability Form" kept up-to-date by the study site staff.
- Unused epineprine auto-injector should be returned to the study site.
- An appointment will be made for Visit 10.

9.3.10 Visit 10 (Post-Treatment Follow-Up Visit)

- This visit is to be performed 14 days ± 7 days after Visit 9.
- Adverse events and concomitant medication will be recorded. A physical examination will be performed depending on medical findings, if any.

9.3.11 Early Termination Visit

In case of Early Termination Visit, all assessments described for Visit 9 are to be done.

In order to avoid missing data, patients who discontinued treatment before the first interim evaluation period (i.e., Visit 5, after 3 months of treatment) will be asked to score their rhinoconjunctivitis symptoms and rescue medication use on the e-diary during the first interim evaluation period, off study treatment.

9.4 Other Supplies

9.4.1 Rescue Medication (Section 8.2.2 "Rescue Medications")

Patients will be supplied with rescue medication by the sites.

9.4.2 Skin Prick Test Kits (Section 9.2.7 "Skin Prick Test")

STALLERGENES will supply the investigational sites with a SPT kit.

The SPT kit will contain:

- Vials of allergen solutions of each of the allergen listed in *Appendix V*,
- Positive control (Histamine dihydrochloride 10 mg/mL) and negative control (saline diluent),
- Pricking device,
- Hypoallergenic transparent tape (Blenderm™),
- Black fine-tip rolling pen.

The allergen solutions and controls are to be stored in the refrigerator at 2°C-8°C.

9.4.3 Blood Sampling Kits (Section 9.2.10 "Blood sampling")

Wherever permitted by local regulations, the sites will be provided with a separate laboratory manual and laboratory kit material. The laboratory manual will contain the sampling, handling and shipment procedures.

9.4.5 Pregnancy Tests (Section 9.2.12 "Pregnancy Test")

The investigational sites will be supplied with urine pregnancy tests by STALLERGENES.

10. ASSESSMENT OF EFFICACY

10.1 Primary Efficacy Variable

The primary efficacy variable will be the average Total Combined Score (TCS). The average TCS is calculated for each patient as the average of the non-missing daily TCSs.

The daily TCS (scale 0-15) is the sum of the patient's daily Rhinitis Total Symptom Score (RTSS, scale 0-12) and daily Rescue Medication Score (RMS, scale 0-3).

The RTSS is defined as the sum of the four rhinitis symptom scores (i.e., itchy nose, sneezing, runny nose, and blocked nose) evaluated daily by the patient. The patient assessment will address symptom intensity over the previous 24 hours and will be performed at the same time every morning, using a 4-point scale (0 = no symptoms; 1 = mild symptoms (symptom clearly present, but minimal awareness; easily tolerated), 2 = moderate symptoms (definite awareness of symptom that is bothersome but tolerable), 3 = severe symptoms (symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping).

If any of the four individual rhinitis symptoms for a given day is missing, then the RTSS for that day will be considered missing.

The RMS is based on the assumptions that an intranasal corticosteroid is more effective than an antihistamine and an oral corticosteroid is more effective than an intranasal corticosteroid, leading

to a derived ordinal scale: 0=absent, 1=oral associated or not with topical (ocular drops) non-sedative H1 antihistamine (H1A), 2= intranasal corticosteroids (INS) with or without oral or topical (ocular drops) H1A, 3=oral corticosteroids with or without INS or oral or topical (ocular drops) H1A.

If rescue medication data for a given day are missing, then the RMS for that day will be considered missing.

The average TCS will be calculated for each patient and each evaluation period as the average of the non-missing daily TCSs during the corresponding period.

10.2 Secondary Efficacy Variables

The following variables will be calculated for each evaluation period (baseline, interim, primary):

10.2.1 Rhinitis Total Symptom Score (RTSS)

The daily RTSS ranges from 0 to 12. The average RTSS is calculated for each patient as the average of the non-missing daily RTSSs during the evaluation periods.

10.2.2 Rescue Medication Score (RMS)

The Rescue Medication Score (RMS) ranges from 0 to 3. The average RMS is calculated for each patient as the average of the non-missing daily RMSs during the evaluation periods.

10.2.3 Adjusted Symptom Score (ASS)

The Adjusted Symptom Score (ASS) ranges from 0 to 12. This score is derived from the daily RTSSs, after adjustment for the patient's rescue medication use. It is patient specific, and will take into account that patients are permitted to make use of any of the three categories of rescue medication [*Grouin et al.,2011*].

The ASS is derived as follows:

- ASS and RTSS are equal the first valid day: $ASS_1 = RTSS_1$.
- If a patient did not take rescue medication at day d and the day before (d-1) then: $ASS_d = RTSS_d$.
- If a patient took rescue medication at day d, the ASS_d will equal the higher value between the RTSS at day d and the ASS of the previous day.

$$ASS_d = \max (RTSS_d, ASS_{d-1})$$

$$ASS_{d+1} = \max (RTSS_{d+1}, ASS_d)$$

Missing data management:

- If the $RTSS_d$ is missing, the ASS_d is missing
- If the information on rescue medication intake is missing, then: $ASS_d = RTSS_d$
- If a patient takes rescue medication at day (d) and $RTSS_{d-1}$ is missing then: $ASS_d = RTSS_d$

The patient estimates the intensity of his/her rhinitis symptoms retrospectively over the previous 24 hours. When he/she takes a rescue medication like antihistamine or nasal corticosteroids, this rescue medication may impact the symptom score assessment on the day of intake and also on the following day. For oral corticosteroids, impact on symptoms probably lasts more than 24 hours and an adjustment for more than 2 consecutive days could be considered. However, by doing so, the adjustment may be overestimated.

The average ASS is calculated for each patient as the average of the non-missing daily ASSs during the evaluation periods.

10.2.4 Combined Symptom and MedicationScore (CSMS)

The CSMS is a score combining the patient's daily RTSS and RMS, assuming equivalent importance of symptoms and medication scores [*Pfaar et al.,2014*]. Since the RMS ranges from 0 to 3 and the RTSS ranges from 0 to 12, the CSMS will be calculated by adding the RMS to the RTSS/4, in order to obtain comparable scales. Thus

CSMS = RTSS/4 + RMS resulting in a daily CSMS ranging from 0 to 6.

10.2.5 Total Ocular Symptom Score (TOSS)

The Total Ocular Symptom Score (TOSS) ranges from 0 to 6. TOSS is calculated as the sum of individual scores for itchy/red eyes and watery eyes (each on a scale 0-3). The average TOSS is calculated for each patient as the average of the non-missing daily TOSSs during the evaluation periods.

10.2.6 Rhinoconjunctivitis Total Symptom Score (RCTSS)

The daily RCTSS ranges from 0 to 18. RCTSS is calculated as the sum of the four rhinitis scores and the two ocular scores (each on a scale 0-3). The average RCTSS is calculated for each patient as the average of the non-missing daily RCTSSs during the evaluation periods.

10.2.7 Six Individual Rhinoconjunctivitis Symptom Scores (RSSs)

The severity of the six rhinoconjunctivitis symptoms (itchy nose, sneezing, runny nose, blocked nose, itchy/red eyes and watery eyes during the previous 24 hours will be scored using a 4-point scale (0: Absence, 1: Mild, 2: Moderate, 3: Severe). The average of each of the six individual RSSs is calculated for each patient as the average of the non-missing daily RSSs during the evaluation periods.

10.2.8 Rhinoconjunctivitis Rescue Medication Usage

The rhinoconjunctivitis rescue medication usage (yes/no), overall and by type of treatment, will be recorded on the e-diary during all the evaluation periods.

10.2.9 Visual Analogue Scale (VAS)

At the end of each week of the evaluation periods, patients will assess the intensity of their allergic rhinitis symptoms using a Visual Analog Scale (VAS), ranging from "absence of symptoms" (score = 0) to "very severe symptoms" (score = 100) [*Jamison et al.,2002; Bousquet et al.,2009*].

The average VAS is calculated for each patient as the average of the non-missing weekly VAS scores during the evaluation period.

10.2.10 Proportion of Symptom-Controlled Days (PSCD)

The PSCD is defined for each patient during the evaluation periods as the proportion of days (%) in the evaluation period where RTSS ≤2 and no rescue medication is used (RMS=0), i.e., $PSCD_{2\text{-}0}$.

This variable will be calculated for the baseline, interim and primary evaluation periods.

10.2.11 Proportion of Not-Controlled Days (PNCD)

The PNCD is defined for each patient during the evaluation periods as the proportion of days (%) with:

- At least one individual rhinitis symptom score = 2 and RMS>0, or
- At least two individual rhinitis symptom scores = 2 whatever the RMS, or
- At least one individual rhinitis symptom score = 3 whatever the RMS

This variable will be calculated for the baseline, interim and primary evaluation periods.

10.2.12 Controlled patients (CP)

Controlled patients are defined as follows:

$CP75_{2\text{-}0}$: Patients with at least 75% of the days with RTSS ≤2 and no rescue medication used (controlled for at least three quarters of the days in the evaluation periods).

This variable will be calculated for the baseline, interim and primary evaluation periods.

10.2.13 Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S)≥12) scores

The RQLQ(S)≥12 consists of 28 questions, divided into 7 domains (activities (3 items), sleep (3), non-nose/eye symptoms (7), practical problems (3), nasal symptoms (4), eye symptoms (4) and emotions (4)), each question being evaluated on a 7-point Likert scale, from 0 to 6 (lower being better). All items are weighted equally. The score for each domain is the mean of the items in that domain (provided that all items of the domain are completed), while the overall RQLQ(S)≥12 score is the mean of all items (provided that the 28 items are completed). The RQLQ(S)≥12 will be used for both adult and adolescent patients.

This quality of life variable will be calculated at Visit 3 (before treatment) and Visit 9 (end of treatment period).

10.2.14 EQ-5D-5L Generic Health-Related Quality of Life Questionnaire

The EQ-5D-5L describes the patients' health state using 5 questions assessing 5 dimensions, namely: 1. Mobility, 2. Self-care, 3. Usual activities, 4. Pain/Discomfort and 5. Anxiety/Depression. Each question is evaluated on a 5-point scale. The patients also self-rate their overall health on a VAS ranging from 0 ("the worst health you can imagine") to 100 ("the best health you can imagine").

This quality of life variable will be calculated at Visit 3 (before treatment) and Visit 9 (end of treatment period).

10.2.15 Global Rating of Change Score (GRCS)

The GRCS measured on the Global Rating of Change questionnaire, is a global assessment of the treatment efficacy compared to the baseline evaluation period on a 15-point Likert scale.

This variable will be assessed at Visit 9 (end of treatment period).

10.3 Other Variables

10.3.1 Work Productivity and Activity Impairment Questionnaire plus Classroom Impairment Questions: Allergy Specific (WPAI + CIQ: AS)

The questionnaire is divided in 3 parts: work performance (4 questions), school performance (4 questions) and impact of allergic rhino-conjunctivitis on the daily activities (one question). Seven scores, expressed as percentages, will be calculated from the questions at baseline (Visit 3) and at the end of the treatment (Visit 9).

10.3.2 Immunological Markers (IgE and IgG_4)

D. pte and *D. far* specific serum IgE and IgG_4 will be assayed at Visit 1 (before treatment) and Visit 9 (after 12 months of treatment).

10.5 Baseline Characteristics

The baseline characteristics are: gender, date of birth, ethnic origin, height, weight, start date of HDM-associated AR, asthma status, FEV_1 measurements, and Skin Prick Tests results.

The following baseline variables will be derived/calculated:

- Age, age class, Body Mass Index (BMI)
- Duration of allergic rhinitis

- Sensitization status (mono- versus poly-sensitivity): derived from the skin prick test results at Visit 1. Patients will be categorized as mono-sensitized if they are positive to HDM (*D. pte* and/or *D. far*) allergens only or poly-sensitized if they are positive to HDM and at least one other allergen
- Average rhinoconjunctivitis symptom and rescue medication scores recorded during the baseline period. Recordings performed before the 4-week baseline period will be considered as training in the use of the e-diary and will be excluded from the analysis
- Rhinoconjunctivitis rescue medication use
- RQLQ(S)≥12 overall score and scores by domain
- Overall assessment of rhinoconjunctivitis symptoms by a VAS
- EQ-5D-5L five questions and VAS score
- Work Productivity and Activity Impairment questionnaire scores plus Classroom questions

The baseline values will correspond to the last evaluation before the first IP intake in the treatment period.

10.6 Methods and Timing for Assessing, Recording, and Analyzing the Efficacy Variables

A one-year treatment period is considered adequate for assessing the efficacy of allergen immunotherapy [*Burks et al.,2013*].Therefore, the primary efficacy variable, the average TCS, will be assessed at the end of the 12 months of treatment.

For specific immunotherapy, onset of efficacy is not expected in the first weeks of treatment. Therefore, in this study, the first interim evaluation period for efficacy is at Month 3.

The methods and timing for assessing and recording the efficacy variables are found in *Section 9* "Study Procedures".

The analysis methods are found in *Section 12* "Statistics".

11. ASSESSMENT OF SAFETY

11.1 Specifications of Safety Variables

The safety variables are adverse events (AEs) and data from the physical examination assessments, vital signs, and safety laboratory tests.

11.2 Methods and Timing for Assessing, Recording, and Analyzing the Safety Variables

The methods and timing for assessing and recording the safety variables are described in *Section 3.6* "Flow Chart" and *Section 9.3* "Visit by Visit Description".

The analysis methods are described in *Section 11.3* "Adverse Events".

11.3 Adverse Events

The Investigator is responsible for recording all AEs experienced by the patient from the time the Informed Consent Form is signed until the patient is discharged from the study.

At each visit, the patient will be given the opportunity to report AEs.

A general prompt will also be given:

"Did you notice anything unusual about your health since your last visit?"

In addition, the Investigator should review all patient self-assessment tools for information regarding AEs.

11.3.1 Definitions

11.3.1.1 Adverse Event

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered an investigational product (IP) and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of an IP, whether or not considered related to the IP.

Signs or symptoms of the condition/disease for which the IP is being studied should be recorded as AEs only if their nature changes considerably or their frequency or intensity increases in a clinically significant manner as compared to the clinical profile known to the Investigator from the patient's history or the baseline period.

In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as an AE rather than the procedure itself.

The following guidelines and definitions should be used by the Investigator for the description of an AE when reporting information.

Nature of the Adverse Event

It should be preferably an overall diagnosis or syndrome, rather than individual symptoms or signs. The Investigator must report AEs using standard medical terminology. The same terms must be used in the source documentation and in the e-CRF. Any discrepancies between the patient's own words on his/her own record (i.e., "AE/Concomitant Medication" card) and the corresponding medical terminology should be clarified in the source documentation.

Assessment of Severity of the Adverse Event

Investigators must assess the severity of AE according to the following qualitative scale. The severity grade does not reflect the clinical seriousness of the event only the degree or extent of the affliction or occurrence (e.g., severe nausea, mild seizure), and does not reflect the relationship to Investigational Product (IP).

- **Mild**: The patient is aware of the event or symptom, but the event or symptom is easily tolerated and not interfering with his/her daily activity.
- **Moderate**: The patient experiences sufficient discomfort to interfere with or reduce his/her daily activity.
- **Severe**: Significant impairment for the patient who is unable to carry out his/her daily activity.

An AE reflecting a change in severity grade should be reported on two separate lines with respective severity grade. The Investigator's original description of the AE must be the same for the first and repeated AE, so that they are coded with the same dictionary term. The outcome date of the first AE should be the same as the start date of the repeated AE, and the outcome of the first AE should be ticked for data management purpose, as resolved.

Example:

Adverse Event	**Severity**	**Start Date**	**End Date**	**Outcome**
Headache	Mild	01-MAR-2012	03-MAR-2012	Resolved
Headache	Moderate	03-MAR-2012	Ongoing	Not Resolved

In the case of local side effects, the grade "severe" should be considered only when these local side effects lead to the permanent discontinuation of the IP [*Passalacqua et al.,2013*].

Occurrence

- **Intermittent:** An AE which occurs repeatedly with the same intensity with an interval of less than 24 hours between occurrences. There are intervals within the specified time period when the AE is not present.
- **Continuous:** The AE is present with the same intensity for the entire time period specified. There is no time at which the event abates or is not present during the time period specified.

Action taken with the Investigational Product following AE occurrence:

- **Not applicable**: For AEs occurring before the IP is administered or occurring after the administration of the IP was stopped.
- **Dose not changed**: IP dosing remained the same in spite of an AE being present.
- **Drug interrupted**: IP usage is temporarily discontinued because of the AE, either because the patient chooses to interrupt the IP or the physician feels it is in the patient's best interest to temporarily discontinue the IP.

- **Drug withdrawn**: IP usage is permanently discontinued because of the AE, either because the patient chooses to discontinue the IP or the physician feels it is in the patient's best interest to discontinue the IP.

Other action taken following AE occurrence:

Any other action taken in response to an AE is to be selected as:

- **None**: No other action was taken for the AE.
- **Medication**: The patient took a medication (either prescription or non-prescription) specifically for the AE.
- **Emergency visit**
- **Therapeutic or diagnostic procedure**: The patient used other therapeutic measures (for example, ice, heating pad, brace or cast) or the patient underwent a diagnostic procedure (for example, additional lab test or X-ray) for the AE.

Outcome at the time of last observation

- **Resolved**: The AE is no longer present at any severity grade - symptoms have completely abated or returned to baseline value in case of worsening of a pre-existing condition.
- **Resolved with sequelae**: The patient recovered from the event but retained pathological conditions resulting from the AE.
- **Not resolved**: The AE has not resolved, and is still present either with the same severity grade (or has not returned to the baseline value in case of worsening of a pre-existing condition) or is improving.
- **Fatal**: The AE directly caused or contributed to the patient's death. In this case a Serious Adverse Event (SAE) form must be completed.
- **Unknown**: There is no information available on the outcome of the AE.

Assessment of Relationship to the Investigational Product

Investigators must systematically assess the causal relationship of AEs to the IP using the following definitions. Decisive factors for the assessment include, but may not be limited to, temporal relationship between the AE and IP, known adverse reactions, medical history, concomitant medication, course of the underlying disease, alternative etiology, etc.

The relationship between the administration of IP and the occurrence of the AE is described as belonging to one of the two following categories:

- **Not suspected**: The event is not suspected to be reasonably related to the IP and could not medically (pharmacologically/clinically) be attributed to the IP. A reasonable alternative explanation must be available.
- **Suspected**: The event is suspected to be reasonably related to the IP and could medically (pharmacologically/clinically) be attributed to the IP.

11.3.1.2 Serious Adverse Event

A Serious Adverse Event (SAE) is defined as any untoward medical occurrence or effect that at any dose:

- **Results in death,**
- **Is life-threatening*,**
- **Requires hospitalization or prolongation of existing inpatients hospitalization**,**
- **Results in persistent or significant disability or incapacity,**
- **Is a congenital anomaly or birth defect,**
- **Is otherwise considered as medically significant***.**

* Life-threatening refers to an event in which the patient was at immediate risk of death at time of event; it does not refer to an event which hypothetically might have caused death if it was more severe.

** The following hospitalizations may not be considered serious:

- Hospitalization planned before entry into the clinical study,
- Hospitalization for elective treatment of a pre-existing condition,
- Consultation in an emergency ward, on outpatient basis and which do not result in overnight hospitalization (unless fulfilling one of the above criteria).

*** Medically significant events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed above (e.g., an event such as bronchospasm that requires intensive treatment but does not result in hospitalization).

Any suspected transmission of an infectious agent via the IP is also considered a SAE.

11.3.1.3 Pre-defined Adverse Event of Special Interest

An Adverse Event of Special Interest (AESI) is a noteworthy event that requires careful monitoring. It could be serious or non-serious.

Special attention should be paid to any symptoms evoking one the 4 following clinical pictures fulfilling the definition of an AESI:

- Severe anaphylactic reactions,
- Severe laryngopharyngeal disorders,
- Autoimmune disorders,
- Eosinophilic esophagitis.

AESIs will be identified and reviewed during the Data Review Meeting (DRM).

11.3.2 Reporting

11.3.2.1 Reporting of AE

All AEs will be actively sought for at each visit. Complete, accurate and consistent data on all AEs, whether spontaneously reported by the patient, discovered by Investigator questioning, or detected through physical examination, laboratory test or other means, will be reported on an ongoing basis in the e-CRF in the "Adverse events" section and followed as appropriate.

If an AE is still present at the time the e-CRF is being locked, a follow-up report shall be provided later on. If no follow-up report is provided, the Investigator shall provide a justification.

If a patient is withdrawn from treatment due to safety reasons, the patient should be followed until the event resolves or the patient's condition has stabilized.

For each AE, the Investigator should specify its nature, start date, time to onset between last IP intake and AE occurrence , duration (if less than 24 hours), stop date, occurrence, action(s) taken with IP, other(s) action(s) taken and outcome. The Investigator should evaluate the event in terms of severity, relationship to IP, and seriousness.

Specific guidance can be found in the e-CRF completion guidelines provided by the Sponsor or designee.

All AEs occurring during the study (from signature of the Informed Consent Form/Assent Form to last visit) must be reported, even if no IP was taken.

Medical conditions present at the initial study visit and that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions, and are NOT to be considered as AEs.

11.3.2.2 Reporting of SAE and Serious AESI

All SAEs including serious AESIs, as defined above, whether or not considered as related to IP, must be transmitted according to the following process:

SAEs including serious AESIs must be reported by the Investigator immediately (i.e., within a maximum of 24 hours of occurrence or Investigator's awareness) by fax or email (relevant contact name, fax number and email address can be found in the Investigator Site File).

The Investigator must duly complete the SAE form even if the data are incomplete or if it is obvious that more data will be needed to draw any conclusions. Reporting procedures and timelines are the same for any follow-up information.

Additional information (e.g., lab data, hospital report) should be provided to the Sponsor or designee in a timely manner to ensure accurate follow-up of each case. SAEs and serious AESIs must be followed up until resolution or until stabilization. If needed, the Sponsor or designee may contact the Investigator to obtain further relevant information regarding a SAE or a serious AESI.

All SAEs and serious AESIs occurring during the study (from signature of the Informed Consent Form/Assent Form to last visit) must be reported even if no IP was taken.

After the end of the study, it is the Investigator's obligation to report to the Sponsor any SAE of which he becomes aware and that he considers as possibly related to the IP, if the SAE occurs up to 30 days after the last IP administration.

SAE occurring after the study

SAEs occurring after the study completion and considered related to the IP have to be reported directly to the Sponsor immediately (i.e., within a maximum of 24 hours of occurrence or Investigator's awareness).

Safety reporting to Health Authorities, Ethics Committees and Investigators

The Sponsor is responsible for complying with the applicable requirements related to adverse experiences by reporting to the appropriate Health Authorities, Ethics Committees and Investigators.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs involving patients to the Ethics Committees that approved the study.

11.4 Unblinding

Under normal circumstances, the treatment blind must be maintained.

In the case of medical emergency in which knowledge of the treatment allocation is considered by the Investigator as critical in managing the patient's condition, the Investigator will utilize IVRS/IWRS and use the unblinding functions. In case of technical issues with the IVRS/IWRS system, the Investigator will contact either the responsible person from the Pharmacovigilance department or primary CRO designee to unblind the patient.

If the blind is broken, the date, the reason for breaking the blind, and person doing so is to be recorded on the source document, and in the appropriate e-CRF page, and STALLERGENES or its representative must be notified immediately. Once the randomization code has been broken, the particular patient's data will no longer be considered eligible for the "*Per Protocol*" set efficacy analysis.

However, when the unblinding was only performed by the Pharmacovigilance department for an adverse event declaration to the regulatory authorities, and not shared with the investigators or study staff, then the patient's data will still be considered as blinded. The patient's data will be valid for the "P*er Protocol*" set efficacy analyses if the patient is otherwise valid.

11.5 Overdose

During the study, any daily intake superior to the dose specified in the protocol will be recorded as a misuse. When the data are unblinded, any daily intake of at least 400 IR will be considered as an overdose.

Symptoms associated with a misuse must be recorded as AEs.

Misuse should be documented in the e-CRF.

11.6 Pregnancy

A newly diagnosed pregnancy itself will not be considered as an AE unless it is suspected that the IP interacted with a contraceptive method or had some association with the occurrence of pregnancy.

A congenital anomaly, spontaneous or therapeutic abortion, stillborn, neonatal death or birth defect as a pregnancy outcome is a SAE.

Before study enrolment, female patients of childbearing potential must be advised of the importance of avoiding a pregnancy during their study participation. Pregnancy should be avoided for the duration of the study so as to ensure that any possible risk to the embryo, fetus and baby be minimized. All females of childbearing potential must be willing to undergo a urine pregnancy test before any IP is administered.

For all pregnancies confirmed after the first IP administration, the Investigator must complete a pregnancy notification form which must be transmitted according to the same process as described for SAE reporting. The Sponsor must be notified without delay. Patient must be withdrawn from the study. Investigators must actively follow-up, document and report on the outcome of all pregnancies, including prenatal and neonatal outcome, even after the patients are withdrawn from the study. Infants will be followed for a minimum of 6 months. Protocol-required procedures for clinical study discontinuation and follow-up must be performed unless contra-indicated by the pregnancy. Other appropriate pregnancy follow-up procedures should be considered if indicated.

11.7 Management of Adverse Events and Patient Discontinuation from Study

11.7.1 Adverse Event Necessitating Temporary Discontinuation of the IP

In case of oral surgery, including dental extraction or any intervention affecting oral mucosa, IP administration should be stopped until complete healing.

Whenever IP has to be discontinued temporarily, IP may be restarted at the dosage of last intake. Should the interruption period be longer than 7 days, it is recommended to restart the treatment under medical supervision, at the dosage of last intake.

11.7.2 Patient Discontinuation from Study

It is ultimately the Investigator's decision as to whether or not to withdraw a patient from the study in case of an AE.

In the occurrence of one of the following events, patients will be systematically discontinued from the study and the IP should be stopped:

- an anaphylactic reaction
- or a severe laryngopharyngeal reaction

- or eosinophilic esophagitis(*) confirmed by characteristic findings on esophagogastroduodenoscopy (EGD) and histologic analysis of EGD biopsies.

(*)Patients with symptoms suggestive of esophagitis will be assessed in accordance with *Appendix VI* "Management of Suspected Esophagitis".

11.7.3 Management of Adverse Events

Management of AEs is at the discretion of the Investigator.

11.8 Independent Data Safety Monitoring Board Review

An independent DSMB will be responsible for assuring that study patients are not exposed to unnecessary or unreasonable risks and that the study is being conducted according to high scientific and ethical standards. Specifically, the DSMB will:

- assess the performance of the study with respect to patient recruitment, retention and follow-up, protocol adherence, and data quality and completeness, in order to ensure the likelihood of successful and timely study completion,
- blindly assess the overall safety and re-assess the risk/benefit of the study on a regular basis.

12. STATISTICS

The statistical methods are summarized below and will be developed and finalized prospectively in the Statistical Analysis Plan (SAP) before unblinding. All analyses will be carried out using SAS® Version 9.4.

Unless otherwise specified, all variables will be summarized descriptively by treatment group (and overall for initial characteristics only) as follows:

- continuous variables will be summarized descriptively using summary statistics (number of subjects, number of missing values, mean, Standard Deviation [SD], 95% two-sided Confidence Interval [CI] of the mean, minimum, lower quartile, median, upper quartile, and maximum).
- categorical variables will be presented using absolute and relative frequencies and 95% CIs for each class of the studied parameter, where appropriate.

For all analyses, the probability of a type I error will be set at 5% and the confidence level at 95% for CI. All inferential tests will be two-sided tests.

In order to control the overall type I error and to draw robust conclusions with regard to the key secondary endpoints, a step-down sequential closed testing procedure will be applied on six secondary endpoints if the primary endpoint is statistically significant. The key secondary endpoints will be tested in the following order:

- 1. Rhinitis Total Symptom Score (RTSS) during the primary evaluation period
- 2. Overall score of Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at the end of the treatment period
- 3. Rhinoconjunctivitis Total Symptom Score (RCTSS) during the primary evaluation period
- 4. Blocked nose symptom score during the primary evaluation period
- 5. Proportion of Symptom-Controlled Days (PSCD, proportion of days with RTSS≤2 and no rescue medication use) during the primary evaluation period
- 6. Rescue Medication Score (RMS) during the primary evaluation period

12.1 Determination of Sample Size

The primary endpoint is the average TCS defined, for each patient, as the average of the non-missing daily TCSs over the last four weeks prior to the end of the treatment period.

[redacted] the clinical relevance of the efficacy results on the primary endpoint is pre-defined as follows [*Nelson et al.,2017*]:

- The relative difference of the TCS *versus* placebo should be ≤-15%, and
- The upper bound of the 95% CI of the TCS relative difference *versus* placebo should be ≤-10%

In the European study VO57.07 [*Bergmann et al., 2014*] conducted in 509 patients, the analysis of the average TCS showed a placebo mean of 3.65 and a relative mean difference of -17% between groups with a 95% CI of [-30% ; -3%]. The CV was of 67% in the placebo group and 77% in the active group.

Based on this 95% CI (i.e., [-30% ; -3%]), an expected relative difference *versus* placebo of -20% was considered as a possible and reasonable value for the true relative difference between both groups. Besides, a CV of 75% was assumed to account for a possible higher variability of the data in this international study (i.e., North America, Europe, Israel and Russia).

Thus, assuming a two-sided nominal level of significance of 5%, a relative difference versus placebo of -20%, a placebo mean of 3.65, and a CV of 75%, simulations were performed based on 5,000 samples and showed that 739 evaluable patients per treatment group were sufficient to achieve a power of around 80% so as to fulfill both requirements (estimated relative difference versus placebo ≤-15% and upper bound of the 95% CI ≤-10%).

Of note, with the same assumptions and 739 evaluable patients per treatment group, the power of detecting a significant difference between both groups is greater than 99%.

Assuming a drop-out rate of 15% during the study, a total of 1,740 randomized patients (870 patients per group) will be required to ensure that 1,478 patients are included in the primary efficacy analysis. The screen failure rate is estimated at 50%, leading to a planned total number of screened patients of 3,480.

12.2 Definition of Clinical Relevance of the Efficacy Results

[redacted] the clinical relevance of the efficacy results on the primary endpoint is pre-defined as follows [*Nelson et al.,2017*]:

- The relative difference of the TCS *versus* placebo should be ≤-15%, and
- The upper bound of the 95% CI of the TCS relative difference *versus* placebo should be ≤-10%

See *Section 12.5.2* "Primary Efficacy Analysis" for the definition of the relative difference and its 95% CI.

Based on historical data obtained with STG320 in study VO57.07 [*Bergmann et al.,2014*], it is expected that the baseline average Total Combined Score (TCS) will be close to 7. Thus, a clinically meaningful effect of 15% in a given patient with an initial TCS of 7 would correspond to an improvement of about 1 point (15% of 7 is 1.08). More specifically, this threshold may be illustrated using e.g., the two following clinical cases:

- With an initial TCS of 7 and a constant RM intake, the patient will benefit from a symptom improvement of 1 point corresponding to a change of one severity class in one symptom e.g., from "severe" to "moderate"
- With an initial TCS of 7 and a stable symptom severity, the patient will experience a decrease of one step in RM intake e.g., s/he will stop the intranasal corticosteroids (from step 2: intranasal corticosteroids with or without antihistamine to step 1: antihistamine) or s/he will not take rescue medication anymore (from step 1: antihistamine to no rescue medication)

This clinical benefit is expected to last all year round as HDM allergic rhinitis induces perennial symptoms.

12.3 Determination of Study Population for Analysis

Safety Set:

The Safety Set will include all randomized patients who received at least one dose of the IP.

All safety analyses will use the Safety Set.

Full Analysis Set (FAS):

In order to be as close as possible to the Intent-To-Treat (ITT) principle, the Full Analysis Set will include all randomized patients who received at least one dose of the IP and have at least one primary efficacy evaluation during a treatment period, (i.e., at least one day with a valid TCS during one of the evaluation periods).

The FAS will be the primary analysis set for all efficacy analyses (primary, secondary, [redacted]).

Per Protocol Set (PPS):

The Per Protocol Set will include all patients in the FAS who complied with the study protocol without any major protocol deviations and had at least 14 days with a valid TCS during the primary evaluation period.

The primary efficacy analysis will be replicated in the PPS.

The definition of protocol deviations (minor or major) will be specified in the SAP. The classification of the protocol deviations as minor or major will be performed during the Data Review Meeting (DRM) before unblinding of the data.

12.4 Handling of Missing and Incomplete Data

Missing data will be handled according to the guideline on missing data in confirmatory trials (Guideline on Missing Data in Confirmatory Clinical Trials EMA/CPMP/EWP/1776/99 Rev.1, 2010).

If any of the individual rhinoconjunctivitis symptom scores or rescue medication data for a given day are missing, the TCS, RTSS, ASS, TOSS, RMS including the missing score(s) for that day will be considered missing. Average scores will be calculated using the non-missing days in the respective evaluation period.

The proportion of valid TCS days during the primary period will be summarized by treatment group in the FAS in order to evaluate the extent of missing TCS data.

In order to prevent missing data, patients who discontinued the treatment before the first interim evaluation period (i.e., before 3 months of treatment) will be asked to continue the study (without study treatment) until Visit 5 (i.e., until the end of the first interim evaluation period). Patients will be asked to score their rhinoconjunctivitis symptoms and rescue medication use on the e-diary during the first interim evaluation period.

In addition, different sensitivity analyses will be investigated and developed prospectively in the SAP, to assess the robustness of the primary analysis with regard to missing data. These include but are not limited to the following:

- Pattern-Mixture Models (PMMs) with reference-based imputation methods using each interim evaluation period and the primary period as repeated measures. These multivariate models implement Missing Not At Random assumptions using multiple imputations
- Mixed Model with Repeated Measures (MMRM) with each interim evaluation period and the primary period as repeated measures. This multivariate model applies a missing at random assumption and is a direct likelihood method in which information from the observed data is used via the within-patient correlation structure to provide information about the unobserved data
- Last Observation Carried Forward (LOCF) as a single imputation method that imputes the last measured outcome value for patients who either drop out or for whom the final outcome measurement is missing

12.5 Efficacy analyses

12.5.1 Evaluation Periods

Rhinoconjunctivitis symptoms and rescue medication use will be recorded daily on the e-diary at the following periods:

- baseline period (placebo run-in): last 4 weeks of the 5-week run-in period
- interim evaluation periods: 2 weeks every 3 months after randomization (i.e., Month 3, Month 6 and Month 9),
- primary period: 4 weeks prior to the end of the treatment period.

12.5.2 Primary Efficacy Analysis

The primary variable, the average TCS, will be summarized descriptively. The square root of the average TCS will be analyzed in the FAS during the primary evaluation period using an Analysis of Covariance (ANCOVA) with treatment group as main effect and pooled center, the square root of the baseline average TCS, age class (adolescent, adult), gender, asthma status (presence/absence) and sensitization status (mono-/poly-sensitized) as covariates.

Patients in the FAS having no efficacy evaluation during the primary period (i.e., no valid assessment) will not be part of the primary analysis. They will be included in the sensitivity analyses to assess the robustness of the primary analysis with regard to missing data.

Due to the high number of centers, a pooling of the centers will be considered to ensure a sufficient number of patients in each treatment group at each level of the covariate "pooled center". The pooling will be performed during the DRM before unblinding of the data and according to the geographic area.

The LS means of square root-transformed average TCS will be assessed in each treatment group. The back-transformed LS means will be calculated in each treatment group. The point estimate, i.e., the LS mean difference, will be calculated from the back-transformed LS means.

The corresponding relative LS mean difference (%) will be derived as follows:

Relative LS mean difference (%) = [(active LS mean - placebo LS mean) / placebo LS mean] * 100

Both the 95% CI for the LS mean difference and the 95% CI for the relative LS mean difference (%), will be calculated using bootstrap method.

Supportive analyses

- The primary efficacy analysis will be repeated in the PPS.
- The average TCS will be analyzed in the FAS during the primary evaluation period using a Wilcoxon rank-sum test (non-parametric method).

Sensitivity analyses

Sensitivity analyses will include PMMs, a MMRM for the four evaluation periods and primary analysis of the average TCS during the primary evaluation period using LOCF method.

Sensitivity analyses are described in *Section 12.4* "Handling of Missing and Incomplete Data".

Summary statistics

The average TCS during each evaluation period will be summarized descriptively and graphically by treatment group in the FAS.

The average TCS during the primary evaluation period will be summarized descriptively per treatment group by each level of each covariate. The average TCS during the primary evaluation period will also be described:

- in the PPS without imputation of missing data

- in the FAS with imputation of missing data using LOCF method

12.5.3 Secondary Efficacy Analyses

Secondary efficacy analyses will be conducted in the FAS.

If the primary endpoint is statistically significant, the six key secondary endpoints will be tested in the following order:

- 1. Rhinitis Total Symptom Score (RTSS) during the primary evaluation period
- 2. Overall score of Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at the end of the treatment period
- 3. Rhinoconjunctivitis Total Symptom Score (RCTSS) during the primary evaluation period
- 4. Blocked nose symptom score during the primary evaluation period
- 5. Proportion of Symptom-Controlled Days (PSCD, proportion of days with RTSS≤2 and no rescue medication use) during the primary evaluation period
- 6. Rescue Medication Score (RMS) during the primary evaluation period

The analysis of the non-ranked secondary endpoints will be considered supportive and will contribute to document the consistency of the study results.

The average of RTSS, RMS, ASS, CSMS, TOSS, RCTSS and each of the six average individual RSSs (calculated as the average of the non-missing daily scores) during the primary evaluation period will be analyzed similarly to the average TCS using the corresponding baseline scores (except PPS analysis and sensitivity analyses). They will be summarized descriptively during each evaluation period.

The proportions of days with rescue medication intake will be summarized descriptively, overall and for each rescue medication category, and analyzed using a Wilcoxon rank-sum test at each evaluation period.

The $PSCD_{2-0}$ and PNCD will be summarized descriptively and analyzed using a Wilcoxon rank-sum test at each evaluation period.

The $CP75_{2-0}$ will be summarized descriptively and analyzed using a χ^2 test at each evaluation period.

The average VAS score (calculated as the average of the non-missing weekly scores), the overall RQLQ(S)≥12 score and RQLQ(S)≥12 scores by domain will be analyzed similarly to the primary efficacy variable using the corresponding baseline scores (except PPS analysis and sensitivity analyses).

The EQ-5D-5L health profile (5 questions) and EQ-5D-5L VAS score will be summarized descriptively.

The GRCS will be analyzed by means of a Cochran Mantel-Haenszel test (row mean score statistic) using pooled centers as a stratification variable. The proportions of improved patients will be compared between groups using a χ^2 test or Fisher exact test.

12.6 Other Analyses

The WPAI + CIQ: AS scores will be summarized descriptively. Percentage of impairment for each score will be calculated and described.

Immunological markers (*D. pte* and *D. far* specific serum IgE and IgG_4) before and after treatment as well as the fold-changes (i.e., the ratio after treatment to before treatment) will be summarized descriptively using number of subjects, number of missing values, geometric mean, 95% confidence interval of the geometric mean, minimum, lower quartile, median, upper quartile, and maximum.

12.8 Safety Analyses

The safety analyses will be performed in the Safety Set.

Safety data will be summarized in the Safety Set by treatment group using descriptive statistics: continuous variables by summary statistics and categorical variables by absolute and relative frequencies.

Adverse events

Adverse events (AEs) will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA).

A Non-Treatment Emergent AE (Non-TEAE) is any AE with a start date on or after Visit 1 and before the first administration of IP in the placebo run-in period, or with a start date at least 31 days after the last administration of IP in the treatment period.

A Placebo run-in Emergent AE is any AE with a start date on or after the first administration of IP in the placebo run-in period and before the first IP administration in the treatment period.

A Treatment-Emergent AE (TEAE) is any AE with a start date on or after the day the first administration of IP in the treatment period was administered and up to 30 days after the date of the last administration of IP in the treatment period, inclusive. If the start date is missing, the AE will be considered as a TEAE. If the end date is missing, the AE will be considered ongoing. The rules of imputation for incomplete dates for AEs will be detailed in the Statistical Analysis Plan.

AEs of Special Interest (AESIs) are defined in *Section 11.3.1.3* "Pre-defined Adverse Event of Special Interest".

An overall summary of all AEs, including the number of events and the number and percentage of subjects with AEs will be provided. Tables by MedDRA System Organ Class (SOC) and Preferred Term (PT) will be provided for Non-TEAEs, TEAEs and for Placebo run-in Emergent AEs.

Additional tables will summarize TEAEs by severity grade and relationship to the IP. Separate tables will also be provided for AESIs, serious TEAEs and TEAEs leading to death, treatment withdrawal or withdrawal from the study.

Detailed subject listings of all AEs will be provided including the onset day and the duration of event (days).

Laboratory values

Laboratory values will be summarized descriptively over Visit 1 and Visit 9 (or Early Termination Visit, ETV), and for the changes from Visit 1 to Visit 9 or ETV. The individual values will be listed with flags for values below and above the laboratory reference ranges.

Pregnancy test

Pregnancy test results will be listed individually.

Physical examination, weight and vital signs

Abnormalities in physical examination will be reported either as AEs or as medical history. Weight and vital signs (systolic and diastolic blood pressure, and pulse rate) will be presented using summary statistics at the screening visit and for vital signs, at the end of treatment visit with changes from baseline to the end of treatment visit (Visit 9).

FEV_1

FEV_1 (L and % of predicted value) will be summarized descriptively at Visit 1 for all subjects and at Visit 3 and Visit 9 for asthmatic patients.

12.9 Baseline Evaluation

Descriptive analysis of baseline characteristics will be presented by treatment group and overall.

Demographic characteristics (age, gender, height, weight, Body Mass Index [BMI]) will be summarized for the Safety Set, the FAS and the PPS.

Baseline characteristics related to the condition (e.g., duration of allergic rhinitis) will be described by treatment group and overall, in the Safety Set, the FAS and the PPS.

Previous and concomitant medical conditions will be presented in the Safety Set as the number of mentions (m), number of subjects (n), and percentage (%) of subjects by MedDRA SOC and PT.

Skin prick tests results [redacted] will be summarized descriptively in the FAS and the PPS.

12.10 Prior and Concomitant Medication Usage Evaluation

Descriptive analysis of prior medication usage will be performed by treatment group and overall. Concomitant medication usage will be described by treatment group.

Prior and concomitant medications will be presented for the Safety Set as the number of mentions (m), number of subjects (n) and percentage of subjects (%) by Anatomical Therapeutic Class (ATC) class Levels 1 and 3.

12.11 Subject Disposition

The number of screened subjects will be presented overall with the reasons for screen failure.

Randomized, treated, completed and discontinued subjects, and subjects allocated to each analysis set will be tabulated and presented in each treatment group.

The subjects who discontinued the treatment and those who did not complete the study will be described, along with a summary of reasons for IP discontinuation and early withdrawal respectively. The subjects who were excluded from an analysis set will be presented with the reasons for exclusion.

Protocol deviations will be listed per subject, describing the nature of the deviation and specifying whether it was a major or a minor deviation. The definition of major and minor will be specified in the SAP and refined during the DRM before unblinding of the data.

The number of subjects at each study visit will be provided.

12.12 Compliance with the Investigational Product in the Treatment Period

Summary statistics for the treatment duration (number of days between the first and the last IP intakes in the treatment period, both inclusive) and the IP compliance (%) will be presented by treatment group for the Safety Set, FAS and PPS.

Overall treatment compliance (%) will be calculated as follows:

$$\frac{\text{('Number of tablets dispensed' – 'Number of tablets returned') x 100}}{\text{'Number of tablets the subjects should have taken'}}$$

The proportion of compliant subjects (overall compliance ≥80%) will be presented in frequency tables in the Safety Set, FAS and PPS.

12.13 Criteria for Unblinding the Results

The DRM will take place:

- after all the data have been verified/coded/entered into the database
- before unblinding of the data

The meeting will be held to decide how to allocate the subjects with protocol deviations or incomplete data (for example missing values, withdrawals, drop outs, non-compliance) to the various analysis sets. The appropriateness of the pooling of sites will be discussed. After the DRM and documentation of all decisions concerning how data issues will be handled, the database will be locked. After database lock and approval of the final SAP, the treatment codes will be requested from the statistician in charge of the randomization.

13. ETHICS

13.1 Approval

The study will not start in a center before the written approval of the corresponding Independent Review Board (IRB) or Independent Ethics Committee (IEC) has been obtained, the local regulatory requirements have been complied with, and the signature of the clinical study protocol of each contractual party involved have been obtained.

The final protocol and subsequent protocol amendments must be submitted to and approved by:

a) Concerned IRB / IEC

b) Relevant Regulatory Authorities, according to local regulations.

Upon receipt, a copy of the IRB's / IEC's written approval (including clear identification of the submitted document(s)) and a list of members attending the meeting) should be forwarded by the Investigator to STALLERGENES. The study is not allowed to start until the protocol and related documents (e.g., informed consent, advertisements) have received written approval from the IRB/IEC and Regulatory Authorities, and all other GCP prerequisites are fulfilled.

The final protocol and any subsequent amendments will be signed by the Principal Investigator of the center, the Coordinating Investigator of the study and the STALLERGENES team members listed on the signature page.

If new important information related to the study or the product become available during the course of the study, it should be communicated without delay to the patients, the Investigators and the IRBs / IECs, and Regulatory Authorities whenever required.

13.2 Patient Informed Consent / Assent

Adequate information will be provided to adult and adolescent patients and parent(s)/legal representatives in both oral and written form and consent/assent will be obtained in writing prior to the patients' participation in the study.

If the patient is <16 years old, an assent form will used instead of the informed consent form. The content and process of obtaining informed consent/assent will be in accordance with applicable regulatory requirements.

An informed consent form or a patient information sheet will be provided to the patients, the parent(s)/legal representatives and an assent form will be provided to the adolescent patients. Each of the two final forms must be approved by the IRB / IEC and must contain all ICH-GCP (Section 4.8.10 of ICH-E6 [R1]) elements in a language readily understandable by the patients, the adolescents or/and their parent(s)/legal representatives.

If the informed consent/assent form is amended during the study, the Investigator must comply with all applicable regulatory and IRB / IEC requirements and use of the amended forms with the on-going and the new patients.

13.2.1 Information

The Investigator, or a person designated by the Investigator, should fully inform the patients and their parent(s)/legal representative, of all relevant aspects of the study. Patients will be informed of the nature, the aim, the procedures, the constraints, the possible risks and expected benefits of the study in a clear and easily understandable language. The patient's participation has to be clearly presented as voluntary and the patient has to understand that s/he will be able to stop, at any time, her/his participation without any consequences for her/his future medical management or treatments. The patient and parent(s)/legal representative must be informed that the anonymity of her/his identity will be guaranteed, especially during the analysis of the patient's personal data. They will be encouraged to ask any questions they may have about the study and they should receive relevant answers. They will receive complete written information on the study in the "Patient Information Sheet".

The Investigator will take into consideration that the parent(s)/legal representative, since they bear the responsibility of the adolescent, might need more detailed and explicit information and hence more time, to consider the expected benefits and potential risks of the study.

13.2.2 Informed Consent / Assent

All the participating patients will have to document their consent to participate in the study by signing and dating an informed consent form. Adolescents from the age of 16 years old are considered of appropriate intellectual maturity and capable of giving their assent to participate in the study and they should personally sign and date the specifically designed assent form. Younger patients will receive the information regarding the study, adapted to the patient's age, and their consent will be sought by the investigators. Adolescent parents/ legal representative will have to sign the informed consent form.

If the signature of a witness is required, the witness should sign and date the consent form, next to the patient's own signature. By signing the consent form, the witness testifies that the relevant information regarding the study was accurately explained to and apparently understood by the patient and that the informed consent was freely given by the patient.

All the forms will also be dated and signed by the Investigator or the designated person who obtained the informed consent/assent according to local regulations. Informed consent procedure will be documented in the patient's medical source data and in the e-CRF.

The patient or/and parent(s)/legal representative will receive a copy of the corresponding form(s) and the original(s) will be filed in the Investigator's Trial File.

The patient may withdraw his/her consent to his/her study participation at any time, without any justification.

A patient is considered as enrolled in the study when he/she or/and his/her parent(s)/legal representative have signed the informed consent/assent form. An e-CRF must not be started, nor may any study specific procedure be performed before having obtained his/her or/and parent(s)/legal representative written consent/assent. The Investigator will keep a patient screening log to document identification of patients who were screened for the study.

If any new information that could influence the patient and/or parent(s)/legal representative decision to remain in the study becomes available, it will be communicated without delay to the patient or/and parent(s)/legal representative.

13.3 Patient Confidentiality

Patient's identification and data confidentiality is to be strictly ensured at any times.

Personnel from the Sponsor (or its representative), from Regulatory Authorities and members of IRB/IEC may inspect patient's medical records and e-CRFs for verification of accuracy of data and have to comply with strict medical secrecy and are forbidden disclosing the patient's identity or any other patient's personal information.

13.4 Informing the General Practitioner

When legally required or if considered as necessary by the Investigator, and if the patient agrees, the Investigator will inform the patient's regular physician of his/her participation in the study, by sending him/her a "letter to the GP" prepared by the Sponsor or the Investigator.

14. STUDY MANAGEMENT AND ADMINISTRATION

14.1 Monitoring

STALLERGENES may subcontract with a Contract Research Organization (CRO) to perform all monitoring responsibilities for this clinical study. The CRO's monitors will work in accordance with the defined monitoring SOPs and have the same rights and responsibilities as monitors from STALLERGENES. Monitors will establish and maintain regular contacts between the investigator and STALLERGENES.

The monitor will advise the Investigator regarding the practical conduct of the study and assist him/her in working according to the protocol, Good Clinical Practice (GCP), and the regulatory requirements.

The Investigator will allow the Sponsor or its representatives to periodically monitor all e-CRFs and the corresponding source documents, at mutually convenient times during the study and after it has been completed. The monitor will have direct access to these records. The monitoring visits provide the Sponsor or its representatives with the opportunity to evaluate the progress of the study, to verify the accuracy and completeness of e-CRFs, to ensure that all protocol requirements, applicable local authority regulations and Investigator's obligations are being fulfilled, and to resolve any inconsistencies in the study records.

14.2 Direct Access to Source Data/Documents

The Investigator(s) and/or Institution(s) will permit study-related monitoring, audits by or on behalf of STALLERGENES, IRB/IEC and regulatory inspector(s), and authorized direct access to source data/documents.

Source documents are original records in which raw patient data are recorded. These may be: hospital / clinic / General Practitioner (GP) records, charts, diaries, X-rays, SPT and laboratory results, spirometry, ECG and other printouts, pharmacy records, care records, completed psychometric scales, diary cards, Quality of Life questionnaires, etc.

Directly entered data in the e-diaries / e-CRF will be considered as source data.

All source documents must be accurate, clear, unambiguous, and readily auditable. They should be generated by using a permanent means of recording (e.g., ink, typing, printing, optical disc).

Hospital/Clinic/Medical files that are computer generated and stored on digital support media should be printable. The Investigator will sign and date the printouts when kept as data source. The Investigator will authorize the monitor to compare the content of the printouts and the data stored in the computer to ensure data consistency.

The minimum requirements for medical source data include the identity of the patient (and any study related identifiers, treatment kit numbers, CRF numbers if used), the patient's participation in the study and identification of the study (e.g., Study Code), the date of obtaining signed informed consent/assent, the dates of the visits, the patient's medical history, the experimental and concomitant treatments, AEs and SAEs and any important relevant information. The source

documents should also provide evidence that inclusion/exclusion criteria were evaluated and met. Information recorded in the e-CRF must be fully consistent with entries in the source documents.

14.3 Audit and Inspection

The Investigator will permit study-related audits by auditors mandated by STALLERGENES, and inspections by domestic or foreign regulatory authorities, after reasonable notice. The main purposes of an audit or inspection are to confirm that the rights and well-being of the patients enrolled have been protected, and that all data relevant for the evaluation of the IP have been processed and reported in compliance with the planned arrangements, GCP and applicable regulatory requirements. The Investigator will provide direct access to all study documents, source records and source data. If a regulatory inspection is announced, the Investigator will immediately inform STALLERGENES.

14.4 Electronic Case Report Forms (e-CRFs)

Electronic case report forms (e-CRFs) will be used for the study and the study site staff will be trained on how to use the e-CRFs and capture the data required by the protocol. The e-CRF is essentially a data electronic entry media and should not routinely constitute the original (or source) medical record.

The Sponsor cannot interpret a blank answer as “NONE” or “N/A”, therefore, all fields must be completed.

Data reported in the e-CRF should be consistent with the source documents or the discrepancies should be explained in these source documents.

The Investigator must complete an e-CRF for each patient who signed an ICF.

It is the responsibility of the Investigator to ensure that the e-CRFs are kept up-to-date so that they always contain the latest observations on the patients enrolled. All supportive documentation submitted to the Sponsor in addition to the e-CRF, such as laboratory results or hospitalization records, must be clearly identified with the study or protocol number, and study patient number. Any personal information, including the study patient’s name, must be removed or rendered illegible to preserve patient confidentiality. The Investigator’s signature of the e-CRF will attest its accuracy and completeness. Study data will be transferred and stored in a clinical database maintained by the CRO. Data recorded by patients in e-Diaries will also be stored in the same clinical database.

14.5 Adherence to Protocol

The Investigator/Institution should conduct the study in compliance with the protocol approved by the Sponsor, the IRB/IEC and, if required, by the regulatory authority(ies) The Investigator/Institution and the Sponsor should sign the protocol to confirm this agreement.

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator will use his/her medical judgment and may withdraw the study patient from the study to prevent immediate hazard. Notification to the Sponsor, its representatives and, if required, the IRB/Ethics

committee will be made regarding the type of emergency and the course of action taken. Significant and/or systematic changes in or deviations from the protocol will ONLY be made as an amendment to the protocol and must be approved in writing by the Sponsor and the IRB/IEC prior to being implemented. Unless the Sponsor has agreed to any such deviations or changes in writing, they cannot be implemented and the Sponsor will not assume any resulting responsibility or liability.

Any significant protocol deviation will be documented and explained by the Investigator or the designated personnel.

14.6 Termination of the Study

Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator, as appropriate:

- transfer of all study data to STALLERGENES or its representative,
- data clarification and/or resolution,
- accountability, reconciliation and arrangements for used and unused study drugs,
- accountability, reconciliation and arrangements for used and unused other supplies,
- review of site study records for completeness,
- discussion/reminder on archiving responsibilities,
- discussion/reminder on investigator's responsibility in case of study audit or inspection.

14.7 Stopping Rules for the study

STALLERGENES reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety (including Data Safety Monitoring Board recommendation) or ethical issues, severe non-compliance, recurrent non-compliance, or unsatisfactory enrolment with respect to quality or quantity.

If the study is prematurely terminated or suspended, STALLERGENES will promptly inform the Investigators/institutions, and the regulatory authority (ies) of the termination or suspension and the reason(s) for the termination or suspension. The information will be shared with the study sites via a formal letter from the Sponsor that will also contain the procedure to manage the practical aspects regarding study patients.

The IRBs/IEC will be promptly informed and provided with the reason(s) for the termination or suspension, as specified by the applicable regulatory requirement(s). In addition, arrangements will be made for the management of all unused IP in accordance with procedures for the study.

14.8 Investigator Site File

The content of the study Investigator Site File is structured in a manner that eases the filing, retrieval, and/or auditing of study-related documents. All documents will be filed according to Standard File Categories that identify specific aspects of the study.

14.9 Data Handling and Record Keeping

Data processing will be subcontracted by the sponsor to the designated CRO.

e-CRF data will be entered in an electronic database using a clinical data management system (CDMS). Computerized edit-checks will be developed in addition to manual review to detect any discrepancies and to ensure consistency of the data. An electronic audit trail system will be used to track all data changes in the database subsequent to the first data entry. The SAS system will be used for the statistical analysis of the data. Regular back-ups of the electronic data will be carried out.

The data of patients who signed an informed consent/assent and underwent any study specific procedures(s) before entering the treatment phase, will be entered in the e-CRF. In case of screen failure before visit 2, only data on demography, adverse events and reason for screen failure will be entered into the e-CRF and clinical database and should therefore be monitored and retrieved from the site.

To ensure data quality all efforts will be made to capture data as soon as they are available. Study sites and patients will be alerted in case data are not submitted in a timely manner.

Sponsor will take advantage of using electronic devices (e-diary, e-CRF) to have a centralized monitoring approach to enhance quality of study data as advocated by National Guidances.

Appropriate actions (e.g., feedback towards study staff in case of repeated inconsistencies) will be undertaken if any missing data, inconsistent data, outlier data and potential protocol deviations are identified during routine remote data review.

14.10 Clinical Study Report

The Sponsor will prepare a clinical study report (CSR) according to the relevant ICH guidelines. The report will include a thorough description of the study, its conduct, efficacy and safety data, statistical analyses and a discussion of the results

The Principal Investigator will receive and review the CSR. He/she must give his/her comments within 30 days of receiving the CSR.

In addition, he/she will sign the CSR for approval within 15 days of receipt of the revised version or a satisfactory reply to these comments.

The CSR and the study data may not be used or communicated by the investigators without prior written approval from the Sponsor.

14.11 Patient Insurance

The Sponsor will contract liability insurance for the total duration of the study, covering the patients with respect to the potential risks related to the study, carried out according to the protocol. In case of injury or disability related to the participation in the study, the patient is to inform the investigator without delay.

14.12 Publication and Presentation Policy

In signing the final protocol, the Investigator agrees to keep all information and results related to the study and the IP confidential. The confidentiality obligation also applies to all personnel involved at the investigational study center.

No unpublished data given to the Investigator may be transmitted to a third party without written approval of the Sponsor.

Publication and communication policy are addressed in the clinical study agreement.

14.13 Archiving and Data Retention

At the end of the study, the Investigator will maintain adequate study records, including e-electronic copies of e-CRF, medical records, laboratory reports, informed consent/assent documents, drug disposition records, safety reports, information regarding patients who discontinued, and other relevant data.

All records are to be retained by the Investigator/Institution until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However these documents are to be retained for a longer period if required by the national applicable regulatory requirement(s) or by an agreement with the sponsor (ICH-GCP Guideline-section 4.9.5).

The Investigator will contact the Sponsor for authorization prior to the destruction of any study records or in the event of accidental loss or destruction of any study records. The Investigator will also notify the Sponsor should he/she relocate or move the study related files to a location other than that specified to the Sponsor.

14.14 Allocation of Responsibilities

The Investigator is responsible for the conduct of the study in compliance with the protocol but can delegate any tasks to his/her research team. He/she remains responsible for selecting his/her staff and for coordinating, training and informing them about the protocol, study procedures and any possible amendments.

The Investigator should maintain a list of appropriately qualified persons to whom each significant study-related duty is delegated using an "authorized signatures" document including name, function, signature, initials, start and end dates of participation in the study conduct and type of delegated tasks.

This list is to be kept current during the entire course of the study.

14.15 Curriculum Vitae

The Investigator should provide his/her updated *Curriculum Vitae* (English version), dated and signed, together with a list of his/her collaborators responsible for the practical conduct of the

study. These designated collaborators should also provide a recent English version of their *Curriculum Vitae*, dated and signed.

14.16 FDA Form 1572 (Statement of Investigator – Mandatory for US)

No Investigator may participate in an investigation (which will be part of an IND) until he/she provides the Sponsor with a completed signed Statement of Investigator (FDA Form 1572). This form is a contractual agreement between the Investigator and the FDA, whereby the Investigator agrees to comply with the study protocol and with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR 312. This form must be updated in the event of a change of facilities or study personnel.

14.17 Financial Disclosure

A financial disclosure statement must be obtained from each clinical site for the Investigator and sub-investigator(s) participating in the study. This will be collected before patient enrollment. The Investigator must inform the Sponsor if information related to financial disclosure changes during the course of the study and for one year after completion of the study.

15. REFERENCES

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